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# TAUTOMERYZM I AKTYWNOŚĆ BIOLOGICZNA β-DIKETONÓW, TRIKETONÓW, β-KETOESTRÓW I β-KETOAMIDÓW. MINI PRZEGLĄD

# TAUTOMERISM AND BIOLOGICAL ACTIVITY OF β-DIKETONES, TRIKETONES, β-KETOESTERS AND B-KETOAMIDES. A MINI REVIEW

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*The work is dedicated to Professor Lucjan Sobczyk on the occasion of the 90th anniversary of his birthday*

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**ABSTRACT**

The review deals with *β*-diketones, *β*-ketoester, *β*-ketoamides, triketones, their tautomerism and biological activity. In addition, it covers briefly methods to detect tautomerism in particular NMR and deuterium isotope effects on chemical shifts, both primary and secondary. A number of typical systems are treated such as: usnic acid, tetracyclines, piroxicam, curcurmines, humulones, acyltetramic acids and quinolone 3-esters.

Keywords: *β*-diketones, *β*-ketoester, *β*-ketoamides, triketones, biological activity, NMR

Słowa kluczowe: *β*-diketony, *β*-ketoestry, *β*-ketoamidy, triketony, aktywność biologiczna, NMR

## LIST OF ABBREVIATIONS AND SYMBOLS

| | | |
|---|---|---|
| DFT | – | Density Functional Theory |
| IR | – | infrared |
| NMR | – | nuclear magnetic resonance |
| ROS | – | reactive oxygen species |
| UV | – | ultraviolet |

## INTRODUCTION

Tautomerism is defined as the movement of a light atom, typically hydrogen, coupled with a rearrangement of the electronic structure. The systems investigated also involve intramolecular hydrogen bonding. A typical examples is that of acetylacetone (Fig. 1). This also demonstrates a common feature, the observation of both the keto and the enol form. Tautomeric equilibria may be slow or fast as demonstrated in Figure 1. The conversion from keto to enol form is slow, whereas the interconversion of the enol forms is ultra fast (femtosecond time scale). The equilibrium between keto and enol form is influenced by the polarity of the solvent. The speed of which the tautomeric forms can be interconverted is of course of interest as some drugs may be acting in a polar environment whereas other will act in a non-polar environment and may be have to change from one form to the other.

In a discussion of structure-activity relationship it is of course important to know the exact structure [1]. Masand *et al.* [2] have discussed the influence of tautomerism on QSAR modeling, but not using compounds of the type discussed here. Examples of neglecting tautomerism is often found in literature. One example is usnic acid, which will be discussed later. The interest in tautomerism in relation to biological activity is increasing. However, some studies are purely theoretical and it should be kept in mind that the molecules are acting in a biological environment (typically a buffer of pH 7.4 and the fact that they should be bio-available). In the present review focus will be on tautomerism that has been established by physical methods.

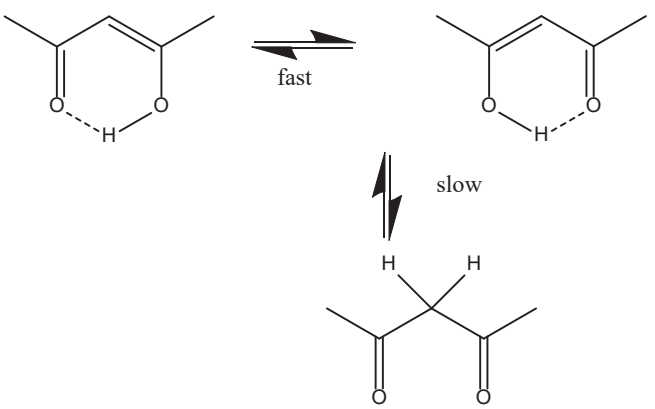



Figure 1. Tautomerism of acetylacetone
Rysunek 1. Tautomeryzm acetyloacetonu

## 1. PHYSICAL METHODS TO DETECT TAUTOMERISM

A good source for information about physical methods and tautomeric equilibria is [3, 4]. So this will be treated very briefly here. "Fast" methods like UV and IR spectroscopy are in principle ideal in the investigation of tautomeric equilibria.

### 1.1. UV SPECTROSCOPY

For the compounds in this review a useful chromophore may be absent. Furthermore, UV spectroscopy is a very sensitive technique and very low concentrations are investigated. This has a number of drawback for compounds with hydroxyl groups as the content of water and oxygen are difficult to control.

### 1.2. INFRARED SPECTROSCOPY

IR should be an ideal way of detecting tautomerism. The strong C=O stretching vibration bands can tell about the number of tautomers and possibly their structure. The OH stretching frequencies are typically red shifted and become for strong hydrogen bonds broad. For a recent discussion see [5]. In practice infrared spectroscopy is not used very much for the compounds discussed in this review. Horta *et al.* [6] used matrix isolation IR spectroscopy, but found only one tautomer (see later). Gromak *et al*. [7] in 3-acyltetramic acid also found one form and possibly one more as shoulders.

### 1.3. NMR SPECTROSCOPY

In case of slow exchange separate signals can be seen in both the $^{1}H$ and $^{13}C$ NMR spectra. A classic example is acetylacetone. This spectrum also demonstrates the fast exchange of the two enol forms, as the methyl signal of the enol tautomers are equivalent (Fig. 2).

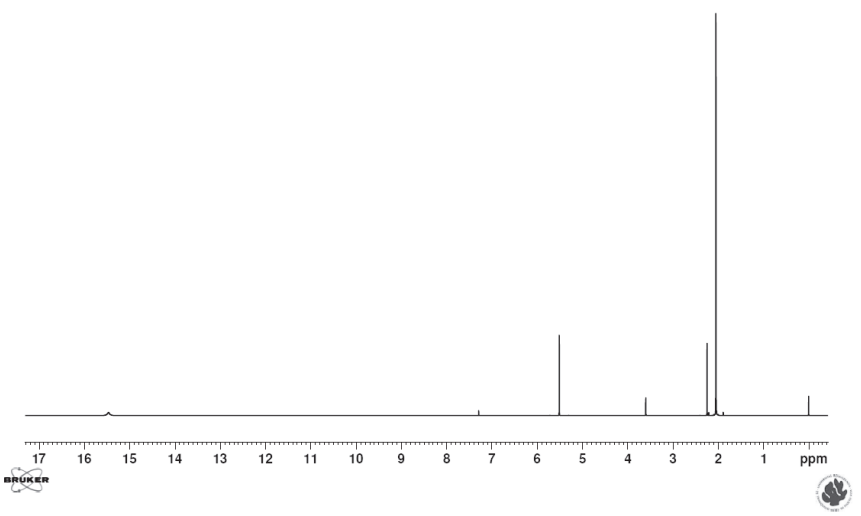



Figure 2. $^{1}H$ NMR spectrum of acetylacetone
Rysunek 2. Widmo $^{1}H$ NMR acetylacetonu

### 1.3.1. Chemical shifts

For non-symmetrical tautomeric systems in fast exchange chemical shifts may often be insufficient to establish the presence of a tautomeric equilibrium. One help is the calculation of the nuclear shieldings of the two tautomers and a fit to experimental data. For examples see [8].

$^{17}O$ chemical shifts is another tool. The very large chemical shift range makes it a strong tool. The disadvantage is the broad lines and the low natural abundance of this isotope [9, 10].

Also Deuterium ($^{2}H$) NMR can be detected, but lines are often broad due to the quadrupolar effects. The natural abundance is also low. In addition, tritium ($^{3}H$) NMR spectroscopy is another way of investigating tautomerism. This of course will require tritium labelling. $^{3}H$ NMR is a very sensitive NMR measurement. As tritium is radioactive special precautions have to be taken to prevent contamination of the instrument.

### 1.3.2. Isotope effects on chemical shifts

Another very useful tool is isotope effects on chemical shifts. In this context deuterium isotope effects on $^{13}C$ chemical shifts and one-bond $^{18}O$ isotope effects on $^{13}C$ chemical shifts as well as five bond deuterium isotope effects on $^{17}O$ chemical shifts and primary deuterium and tritium isotope effects are discussed.

In equilibrating systems isotope effects can be expressed in a simple way exemplified for deuterium as the isotope and $^{13}C$ as the nucleus for detection:

$$\Delta C_{total} = X_M \, \Delta C_{int}(M) + (1 - X_M) \, \Delta C_{int}(PT) + \Delta XH(D) \, (\delta C_M - \delta C_{PT}) \qquad (1)$$

The first term is the intrinsic isotope effects in which the two forms and the mole fractions are taken into account. Intrinsic isotope effects behave very much like substituent effects. The second part is the change in the chemical shift due to a change in the equilibrium constant due to deuteriation. The last term is seen to depend on the chemical shift difference between the equivalent carbons in the two tautomers. This means that this term can both be large and of both signs.

#### 1.3.2.1. Two-bond deuterium isotope effects on $^{13}C$ chemical shifts

It is also found that the formally two-bond isotope effects can be plotted against the equilibrium constant leading to a S-shaped graph (Fig. 3) [11].

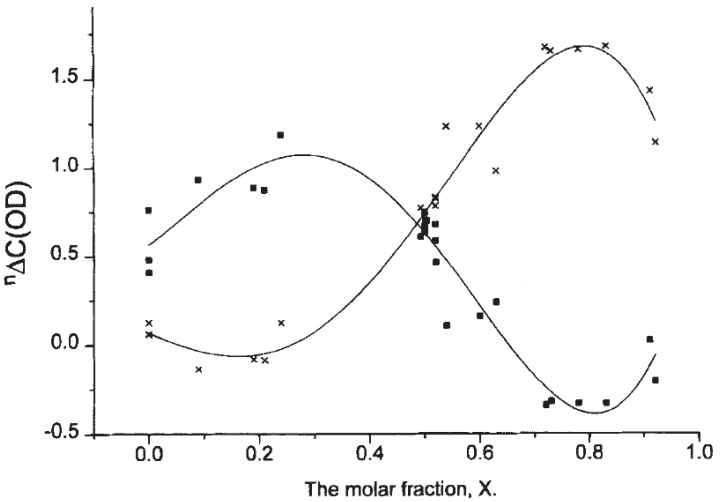



Figure 3. A plot of the two-bond deuterium isotope effects on $^{13}C$ *vs* the mole fraction. (From ref. 11, reproduced with permission from John Wiley and Sons)

Rysunek 3. Zależność wpływu efektów deuterowania poprzez dwa wiązania na $^{13}C$ w zależności od ułamka molowego. (Z pracy 11, przedruk za zgodą John Wiley and Sons)

### 1.3.2.2. One-bond $^{18}O$ isotope effects

It has been shown that one-bond $^{1}\Delta^{18}O^{13}C$ isotope effects are distinctly larger for double bonds [12] than for single bonds [13] (Fig. 4).

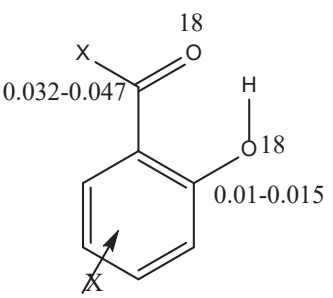



Figure 4. One-bond $^{18}O$ isotope effects on $^{13}C$ chemical shifts

Rysunek 4. Efekty izotopowe $^{18}O$ na przesunięcia chemiczne $^{13}C$

They follow in other words the bond order as previously demonstrated by Jameson [14]. In case of hydrogen bonding $^{1}\Delta^{18}O^{13}C$ decreases slightly [12]. For double bonds also the isotope effects are slightly different for ketones, aldehydes and amides [13].

### 1.3.2.3 Five-bond deuterium isotope effects on $^{17}O$ chemical shifts

Five-bond deuterium isotope effects on $^{17}O$ chemical shifts, $^{5}\Delta^{17}O(D)$ – these isotope effects have been used among other things to distinguish "static" from equilibrium systems [15].

### 1.3.2.4. Primary isotope effects

Both for deuterium and for tritium primary isotope effects, defined as: $^{P}\Delta^{1}H,^{2}H$ and $^{P}\Delta^{1}H,^{3}H$ can be measured. For tautomeric systems these show the same features as $^{2}\Delta^{13}C(OD)$ isotope effects [16]. Negative primary deuterium isotope effects were taken by Altman et al. [17] as a sign of a single potential well. This is fine as long as the isotope effect is solely intrinsic, whereas for equilibrating systems negative isotope effects may easily be obtained.

## 2. COMPOUNDS

### 2.1. USNIC ACID

One of the interesting triketone systems is usnic acid. Usnic acid exists in two enantiomeric forms. One is isolated from lichens and is easily available. Several different structures have been proposed, one of which is the keto-form in Figure 5.

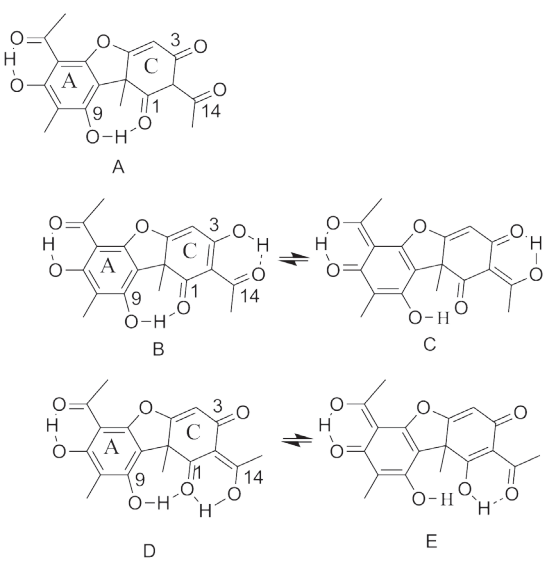



Figure 5. Tautomeric forms of usnic acid
Rysunek 5. Formy tautomeryczne kwasu usninowego

However, it has been shown to be tautomeric with no presence of the keto-form [18]. A useful tool, as described in the NMR chapter 1.3.2, is deuterium isotope effects on chemical shifts. The finding that the deuterium isotope effects at both $C{=}OCH_3$ and C-3 are close to being identical demonstrates a 1:1 mixture in $CDCl_3$ as seen in Figure 6.

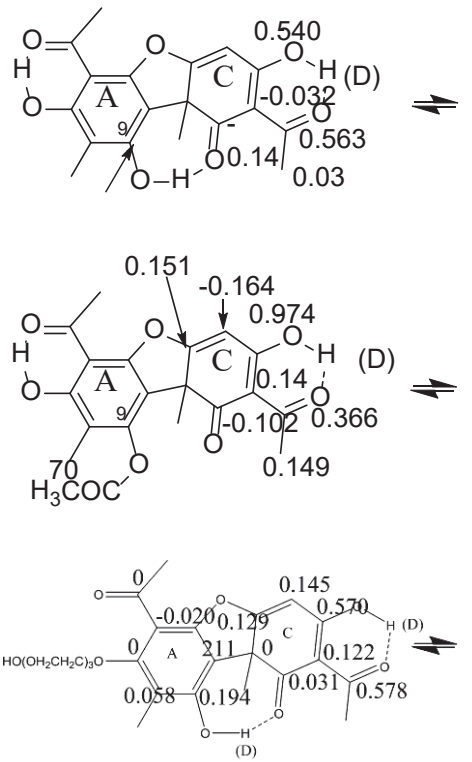



Figure 6. Deuterium isotope effects on $^{13}C$ chemical shifts of usnic acid (A), acetylated usnic acid (B) and pegylated usnic acid (C)

Rysunek 6. Efekty deuterowania na przesunięcie chemiczne $^{13}C$ kwasu usninowego (A), acetylowanego kwasu usninowego (B) i „pegylowanego" kwasu usninowego (C)

One drawback is the low solubility of usnic acid in water. To improve the water solubility usnic acid was pegylated at the OH-7 group. This has no effect at the equilibrium in a mixed DMSO/$D_2O$ solvent (Fig. 6) Usnic acid has many useful biological functions such as antimicrobial, antiviral, antiprotozoal, antimitotic, anti--inflammatory and analgesic activity [19, 20] and it has unfortunately been used as slimming powder. The biological activity is believed to be linked to ring C [21], the ring with the triketo moiety. An interesting observation is the change this equilibrium as the OH group at C-1 is acetylated. In Figure 6 a large change in the isotope effects at $C{=}OCH_3$ and C-3 is seen as compared to usnic acid itself. Another interesting point is the high acidity of the enolic proton, $pK_a$ value of 4.4 [1, 22]. This

should of course be taken into account when discussing the structure. However, for the DMSO-$D_2O$ mixture this proton is not lost as the isotope effects would have been much smaller or absent (see Chapter 2.2 on tetracycline).

### 2.2 TETRACYCLINE

Tetracycline is a well known antibiotic and now primarily used in large amounts in pigs fodder. The risk of resistance is therefore high. The structure is complex as seen in Figure 7 and a large number of tautomers and zwitter ionic forms can exist. Duarte *et al.* [23] have drawn sixty four. A very large number of papers have been dealing with the structure of tetracycline over the years and are not all referred to in this review.

In this context two regions are of particular interest, the externally hydrogen bonded $\beta$-diketone system linking rings D, C and A and a formally ketoamide system in ring A. Add to that the secondary amine in ring A. The structure of the hydrogen bonded $\beta$-diketone system can be determined based on deuterium isotope effects on chemical shifts (Fig. 7) as seen from a comparison with a model compound (Fig. 8).

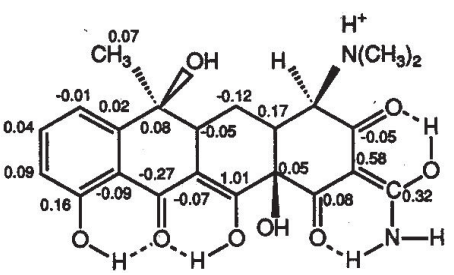



Figure 7. Deuterium isotope effects on $^{13}C$ chemical shifts of tetracycline in a water:DMSO (1:1) mixture at pH 6.3 [24].

Rysunek 7. Efekt deuterowania na przesunięcie chemiczne $^{13}C$ tetracykliny w mieszaninie woda:DMSO (1:1) przy pH 6,3 [24]

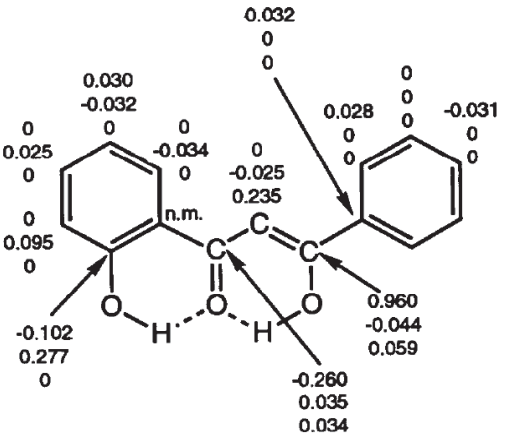
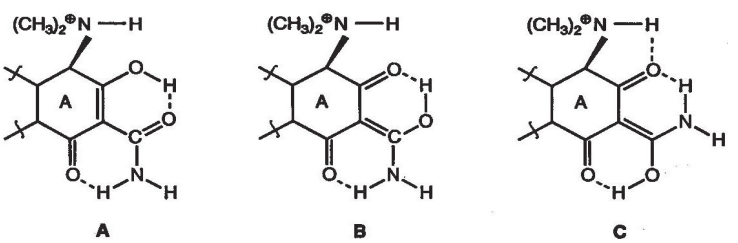



Figure 8. Deuterium isotope effects on $^{13}C$ chemical shifts of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3--dione [24]. Only the most populated tautomeric form is shown. (With permission from Elsevier)

Rysunek 8. Efekt deuterowania na przesunięcie chemiczne $^{13}C$ 1-(2-hydroksyfenyl)-3-fenylpropane-1,3-dione [24]. Przedstawiono tylko najczęściej występujący tautomer. (Za zgodą Elsevier)

From these data it can be concluded that the equilibrium is shifted very strongly towards one side as seen in Figure 8.

The equilibrium at the A-ring is more complicated as shown in Figure 9.




A B C

Figure 9. Tautomeric structures. Only the A ring is shown

Rysunek 9. Struktury tautomeryczne. Przedstawiono tylko pierścień A

A similar system has been investigated as shown in Figure 10.

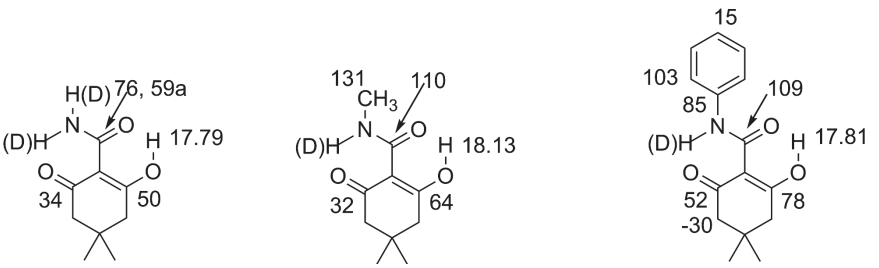



Figure 10. Deuterium isotope effects on $^{13}C$ chemical shifts of 2,6-cyclohexanediketo-1-amides [25]. Values for isotope effects in ppb and values for OH chemical shift in ppm. a refer to the isotope effects from the non-hydrogen bonded NH(D). (Reproduced with permission from Elsevier)

Rysunek 10. Efekt deuterowania na przesunięcie chemiczne $^{13}C$ 2,6-cykloheksanediketo-1-amidów [25]. Wartości efektów izotopowych w ppb a przesunięcia chemicznego OH w ppm. a odnosi się do efektów izotopowych NH(D) nie uczestniczącego w wiązaniu wodorowym. (Przedruk za zgodą Elsevier)

From the deuterium isotope effects on $^{13}C$ chemical shifts of tetracycline a number of findings can be extracted immediately. A very large effects is seen at C-2 of the model compound due to deuteriation at OH-2 (showing the enolic form). No such effect is seen in tetracycline. This rules out structures A and C of Figure 9. The isotope effects observed in tetracycline are in fair agreement with structure B as judged from a comparison of ND isotope effects as seen in Figure 10. However, the effect of 0.12 ppm at C-3 of tetracycline suggests that an equilibrium between structures A and B exits, with the latter dominating [24].

Oxytetracycline has also been investigated. In that case one-bond $^{18}O$ isotope effects at C-1 and C-3 of 0,032 and 0,034 ppm are reported [26]. This strongly indicates that both carbon 1 and 3 are of C=O type.

The viricatum toxin (which is similar to tetracycline) shows a one-bond $^{18}O$ isotope effect of 0,019 ppm at the $CONH_2$ carbon [27]. This is somewhat smaller than amides (0,029 ppm) and shows a considerable amount of single bond in good agreement with a structure like B.

## 2.3. CURCURMIN

Curcurmin and its derivatives are extended $\beta$-diketones systems and as such tautomeric. Hundreds of papers have been publishes on the biological effects of curcurmin and derivatives. Most interestingly related to cancer and Alzheimer (see later). These hundreds of papers do not deal with tautomerism and cannot be referred to here. Only a couple of examples are given. An important feature is if both the ketone and the enol form is present.

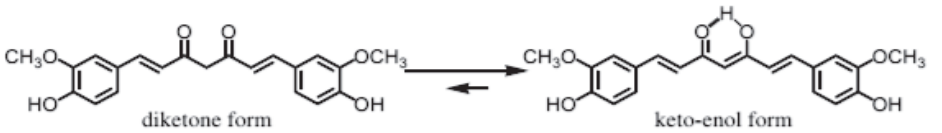



Figure 11. Tautomerism of curcurmin
Rysunek 11. Tautomeryzm kurkuminy

In the case of substituted curcurmines (Fig. 12) it was found that the compounds with a keto-form bound better to the A,*β* amyloid than to the monomer, indicating than these compounds could be a useful drug against Alzheimer disease [28].

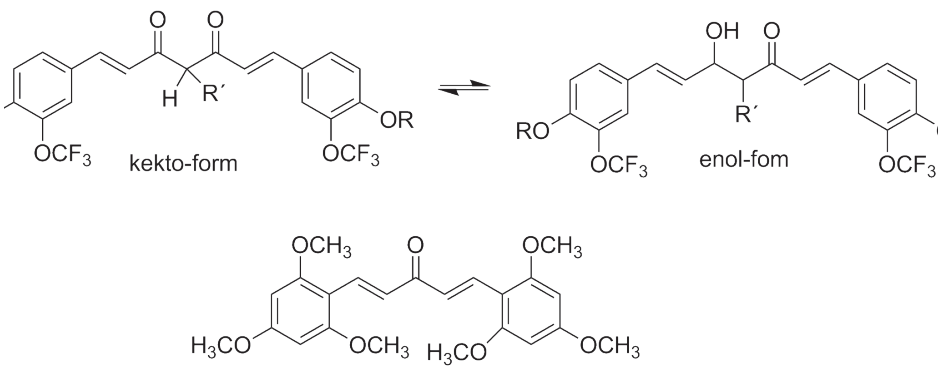



Figure 12. Curcumin derivatives
Rysunek 12. Pochodne kurkuminy

Fan *et al*. also found curcumin to suppress A*β*-induced cytotoxicity and apoptosis by inhibition of the ROS-mediated oxidative damage [29]. Fuchs *et al.* [30] made a structure- function relationship study of a series of twenty compounds to finds that the lower structure of Figure 12 was the most active against both prostate and breast cancer cell lines.

Ali *et al.* [31] call the compound of Figure 8 for a curcumin derivative, which is a bit far fetched. They found that the compound induced apoptosis through accumulation of intracellular ROS in MCF-7 breast cancer cell. The accumulation is contrary to what Fan *et al.* (see above) found.

### 2.4. 3-ACYLTETRAMIC ACIDS

These have a *β*-diketone structure (Fig. 13) and show interesting biological effects and have been reported to show tautomerism. Jeong *et al*. [32] found that for NH and NR systems form D was dominant with a small amount of B, whereas for the *N*-acyl derivatives a 50:50 mixture between A and D forms were found.

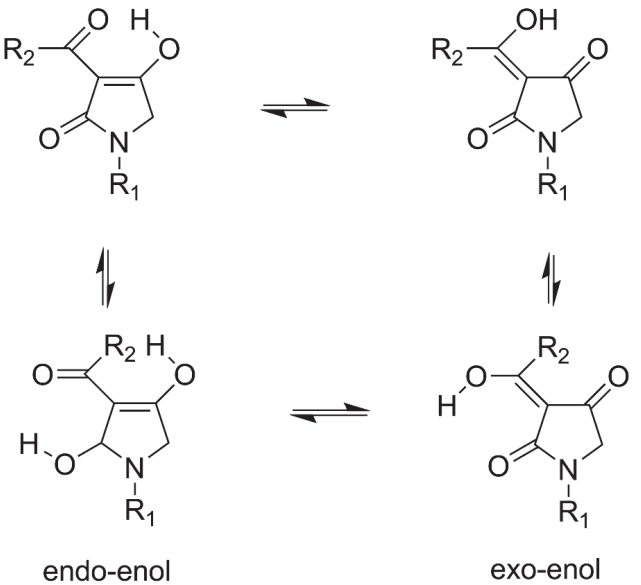



Figure 13. Tautomeric forms of 3-acyltetramic acids
Rysunek 13. Formy tautomeryczne kwasów 3-acylotetramowych

In another case biological activity was reported, but the possibility of tautomerism was not explored [33].

### 2.5. HUMULONES AND HOP ACIDS

They are triketones as seen in Figure 14. In non-polar organic solvents they show tautomerism, whereas in polar solvents the equilibrium is at one side (Fig. 14). An example is colupulone as shown in Figure 14.

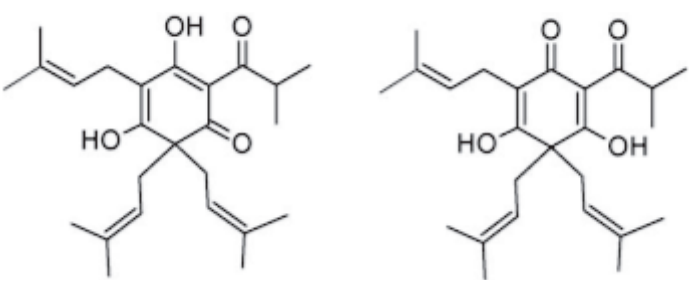


Figure 14. Tautomeric structures of colupulone (from ref. 34, reproduction with permission from Elsevier)
Rysunek 14. Struktury tautomeryczne kolupulonu (z pracy 34, przedruk za zgodą Elsevier)

Lupulone is very similar with a $CH_2CH(CH_3)_2$ side-chain instead of the $-CH(CH_3)_2$ side chain. Lupulone inhibits cell growth and induces caspase dependent apoptosis [34].

Another triketone is epiclusianone, a polyisoprenylated benzophenone (Fig. 15). It has biological activity such as anti-inflammatory, anti-tumor and anti-oxidant properties. As seen in Figure 15 Lage *et al.* [35] have calculated structures. The tautomeric forms b,c were found in chloroform and benzene. Different DFT functional gave different results. The wB97x-D functional reproduced the experimental findings best. In methanol, DMSO and acetone the d-form was predicted.

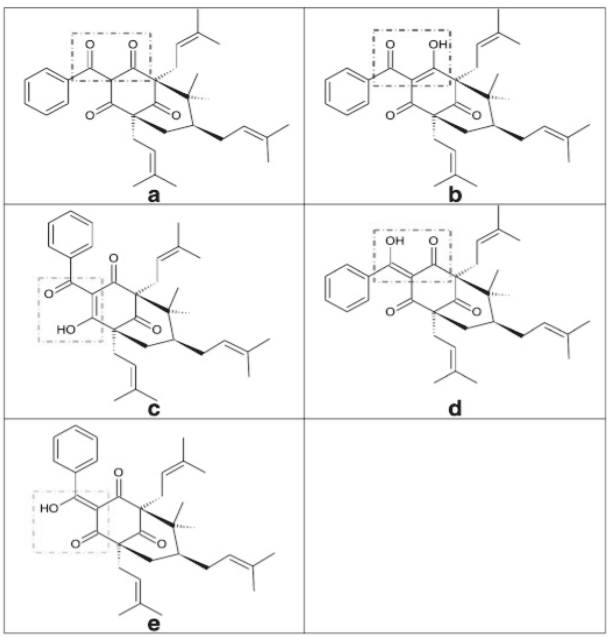



Figure 15. Tautomers of epiclusianone (from ref. 35, reproduced with permission from Springer)
Rysunek 15. Tautomery epiklusianonu (z pracy 35, przedruk za zgodą Springera)

### 2.6. PIROXICAM

Piroxicam is a non-steriodal anti-inflammatory drug (NSAID) drug and is good against arthritis and recent studies show that it may active in colorectal cancer [36].

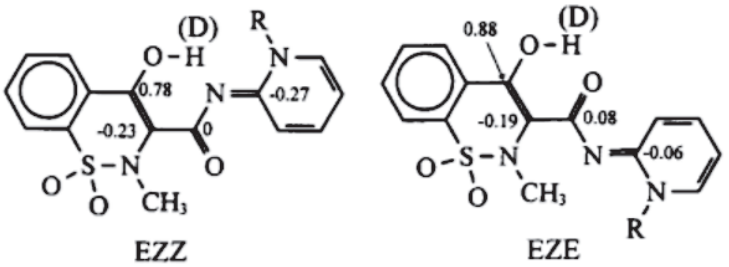



Figure 16. *Cis-trans* structures of piroxicam [37]
Rysunek 16. Struktury *cis-trans* piroksykamu [37]

The structure is formally a $\beta$-ketomamide. Cis-trans structures were found by Bordner *et al.* [37] as shown in Figure 16. As the following will show this is only partially correct. A number of tautomers can form formulated as seen in Figure 17.

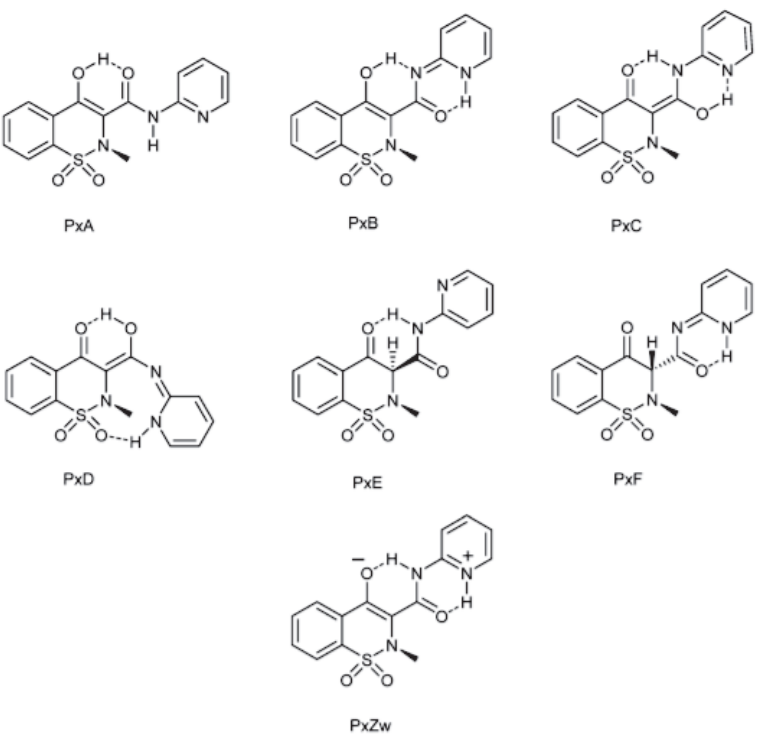



Figure 17. Calculated tautomers of piroxicam
Rysunek 17. Obliczone tautomery piroksykamu

In $CDCl_3$ piroxicam was found to be a dimer of monomers with PxA structure. In DMSO-$d_6$-$H_2O$ deuterium isotope effects gave the following picture [38].

As seen from Eq. 1 and assuming that the equilibrium contribution is dominant, we arrive at the following equation:

$$\Delta C_{equi} = \Delta X_{H(D)} (\delta C_M - \delta C_{PT}) \quad (2)$$

The isotope effects should be proportional to the chemical shift differences of equivalent carbons. These differences can be calculated. Such a picture is seen for the majority of the carbons (Fig. 18). Those point falling outside belong the carbons C-11 and C-12. For the latter two this proves that the pyridine is protonated (deuteriated) in order to give a large intrinsic contribution leading to a point outside the line for carbons with mainly equilibrium contributions. We find an equilibrium between the Pxa form (hydrogen at OH- leading to C-7 and C-9 falling off the line) and Pxzw.

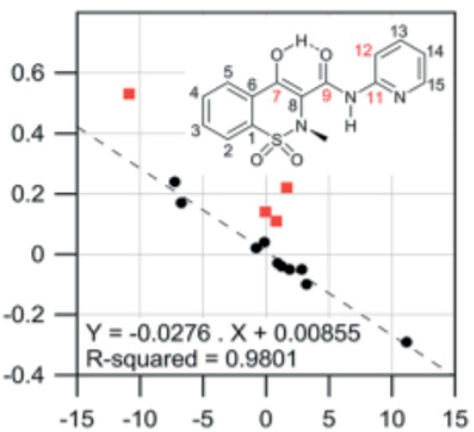



Figure 18. Deuterium isotope effects of piroxicam vs. calculated $^{13}C$ chemical shift differences between the PxA and Pxzw forms. Data for C-7, C-9, C-11 and C-12 atoms are given in red squares. (From ref. 38, reproduced with permission form the Royal Society of Chemistry)

Rysunek 18. Efekt deuterowania piroksykamu w funkcji obliczonych różnic przesunięcia chemicznego $^{13}C$ pomiędzy formami PxA i Pxzw. Wartości dla atomów C-7, C-9, C-11 i C-12 przedstawiono czerwonymi kwadratami. (Z pracy 38, przedruk za zgodą Rogal Society of Chemistry)

### 2.8. QUINOLONE 3-ESTERS

The quinolone-hydroxyquinoline 3-esters have a structure akin to a $\beta$-ketoester, but the tautomerism is induced *via* the NH proton. The depicted compounds are active against malaria. Docking studies showed that the NH-form was important for the inhibitory activity towards *P.-falciparum* b1 protein complex. However, it is the OH-form that is found in solution [39]. The authors have been able to synthesize the NH-form. The question is if this still exists after a trip through the stomach, intestines and blood.

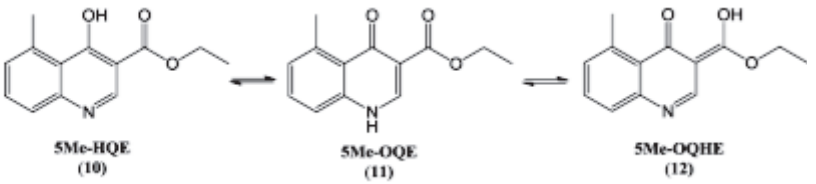



Figure 19. Possible tautomers of the 5-methyl derivative
Rysunek 19. Możliwe tautomery 5-metylopochodnej

## FINAL REMARKS

Many compounds with biological effects show tautomerism. It is of course in the search for the mechanism important to know the exact structure. This is also essential in attempts to synthesize molecules with even better properties. The present review covers only a small corner of all tautomeric compounds, namely the "$\beta$-diketo" type.

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