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Review Article

Coordination Compounds of M(II) Biometal Ions with Acid-Type Anti-inflammatory Drugs as Ligands – A Review

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Abstract

The cations of biometals in biological systems easily interact with various moieties of organic and inorganic biomolecules, either as natural constituents or after introduction into the body via O-, N- and S- donor atoms. Study of the interaction between M(II) biometal–O-donor ligand (drug) is of interest for various reasons: more evenly dosing of medicine and biodistribution of medicine; monitoring of its pharmacokinetics including excretion; reduction of unwanted effects of the medicine; greater antimicrobial activity; synergistic effect of the metal and medicine; and improved anti-ulcerous, anti-tumor and anti-bacterial activity. This paper offers an overview of the literature of published research on coordination between biometals and anti-inflammatory drugs of the acid type. The metals that the subject of focus in this review are d-metals with M(II) ions, namely, copper (Cu), zinc (Zn), cobalt (Co) and manganese (Mn).Those containing molecules with carboxyl functional groups can build complexes with coordinated number of metals of 4 and 6, of various stoichiometric structures, simple or complex, and also behave as monodentate, bidentate or bridge ligands in polynuclear complexes.

Keywords: *Biometals M(II), Anti-inflammatory medicine, Coordination, O-Donor ligands, Copper, Cobalt, Manganese, Zinc*

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INTRODUCTION

Biometal cations in biological systems easily interact with molecules of water and various parts of different organic and inorganic biomolecules, as natural constituents or substances introduced into the human body. The complex associates, built via O-, N- and S- donor atoms, have an important role in biological processes. The products of interaction between M(II) metals and medicine are fundamentally important for the theory of coordination chemistry, as well as the significance of the development of new methods for determining micro-amounts of active components [1-3].

The study of the interaction between M(II) *biometal–O-donor ligands* (the drugs) is interesting for a variety of aspects, with the aim of: achieving more balanced medicine dosing, the biodistribution of the medicine; monitoring its pharmacokinetics, excretion; the reduction in the unwanted responses; improving anti-microbial activities; synergistic effects of the metals and medicine, and improved anti-ulcerous, anti-tumor and anti-bacterial activity [4-11].

The mechanisms of the effects of biometal complexes are diverse. The complex biometal compounds, in addition to a beneficial have a toxic effect on the body, which often limits their application [12]. A pioneer in the study of the complexes of transition metals and non-steroid anti-inflammatory drugs (NSAIDs) was Sorensen [13]. The literature is replete with numerous data on studies on the interaction between M(II) ions of metals and numerous ligands of pharmaceuticals and supplements via O-, N-, S-donor atoms, as well as the synthesis of their products and the effects which the obtained products lead to [4-11].

M(II) BIOMETALS

Biometals from the series of d-metals with characteristic M(II) ions can be found in the human body in small amounts, and are mainly the active centers of enzymes of various functions. They are introduced into the body daily through a variety of food, which satisfies the daily requirements (Table 1) [12].

Biological role of copper

Back in 1920, it was shown for the first time that copper is essential for biological systems. That was when it was discovered that anemia among experimental animals occurs as the result of a decreased intake of copper as a part of their regular diet. With the addition of copper salts, there was a correction in the occurring pathological state [20,21]. In the biological processes of living organisms, copper plays an important role in the process of binding oxygen, redox processes, electron-transfer processes, and is a part of the structure of numerous enzymes: enzymes for the transport of electrons and the enzymes which take part in processes of oxygenation, among others [3,22]. Copper uses numerous enzyme systems to participate in the various processes in the human body (hemoglobin formation, the metabolism of carbohydrates, the biosynthesis of catecholamine, antioxidative protection of the human body, the reduction in reactive oxygen types [23]. Copper plays an important role in the reduction of inflammatory processes, and achieves this role through enzyme superoxide dismutase (SOD) [20]. Copper is necessary for the synthesis of hemoglobin [24].

Of the overall content of copper in the human body, most of it is found in the human skeletal system, liver, brain and blood. Under normal physiological conditions, the human body contains 80-120 mg of copper [12]. The daily requirements of the human body for copper, on the basis of the recommendation of the World Health Organization, ranges in the interval from 0.9 to 1.3 mg/day [15]. Disorders related to the copper contained in the human body are related to the occurrence and development of certain illnesses (aceruloplasminemia, Wilson's disease, Menkes disease, Alzheimer's, various inflammatory processes in the human body, tumors, etc) [23]. Approximately 50 % of the overall intake of copper is absorbed through the bloodstream, and bound to albumins is transferred to other organs and tissues [25].

The various roles of this biometal in living organisms are bound, on the one hand, to its polyvalent nature, and on the other, to the tendency of its ions to build complex compounds. In the theory of coordination compounds, it is well known that the Cu(II) ion, d^9, builds coordination compounds with a coordination number of 4 or 6, including quadri-planar, tetrahedron or deformed octahedron structures. The content and structure of the chelate products depend on the physical-chemical features of the ions (size, polarizability, ion potential, acidity) and the size of the ligand and the active centers, potential atom donors, denticity, etc. The possible content of the complex associates has a coordination number of 4 or 6 and can be matched to the formulas $[ML_4]$, $[M(L\text{-}L)_2]$, $[ML_4X_2]$, $[M(L\text{-}L)_2X_2]$. At the same time they can be mononuclear, binuclear or polynuclear. Binuclear Cu-active centers play an important role in biological metalloproteins (tyrosinase, hemocyanin, catehol oxidase...) [3,26].

Table 1: M(II) biometals in the human body (numbers in parenthesis denote references)

Biometal	Body content	Blood content	Target organs	Daily requirement (mg/day)
Cu	80-120 mg [12]	0.8-1.6 mg/L [14]	skeletal system,muscles, brain, liver	0.9-1.3[15]
Zn	2-3 g [12]	6.3 mg/L [14]	pancreas, bones, teeth, liver, kidneys	2-15[15]
Co	3 mg [16]	0.39 µg/L [14]	liver, pancreas, kidney, heart	1.5*[17]
Mn	12 mg [16]	4-15 µg/L [18]	liver, pancreas, kidney,	2-5 [19]

In the form of vitamin B12 (egual of 0.006 mg of Co)"

Biological role of zinc

Zinc is a biometal necessary for the growth and development of mammals, and in the human body, approximately 2 to 3 g of this metal can be found in the structure of more than twenty metalloenzymes (carbohydrase, alcohol dehydrogenase, Cu-Zn superoxide dismutase, etc). Zinc ion along with the Cu(II) and Co(II) ions improves the immune system of humans. If enough zinc is introduced into the human body in doses larger than the recommended daily dosage, negative effects, such as disorders of iron depots and decrease in the life expectancy of erythrocytes which leads to anemia and greater use. On the basis of the data found in the literature, zinc in concentrations greater than 800 mg/daily causes a significant increase in the amylase and lipase in the serum, and the increase in the level of glucose in the blood [27].
Based on the size and physical-chemical features of the Zn(II) ion, of the d^{10} electron configuration, it easily interacts with parts of the biomolecules, mainly via the O-donor atoms of amino acids, proteins etc. At the same time, it builds compounds with a coordination number 4. According to the denticity of the ligand, its content can be found in an M:L = 1:4 ratio, that is, 1:2, with the possible inclusion of solvent molecules [3,26].

Biological role of cobalt

Cobalt as a micro-element has a role in the metabolism of proteins and amino acids for the transfer of methyl groups from the methyl donors to the methyl acceptors as the constituent parts of metaloenzymes (methyltransferase and methionine transferase) [12]. Via vitamin B_{12} [29], which plays an important role in the process of erythrocyte maturation, Co increases the use of iron in bone marrow cells [24]. Absorption of Co from food in the human body depends on the individual's diet, for example the presence of amino acids decreases, while iron deficiency increases [17,29]. Co(II) ion also causes apoptosis of the cells, and in greater concentrations even necrosis with an inflammatory response. In addition, this metal has a genotoxic influence [29]. Co(II) ion of the d^7 electron configuration, easily interacts with moieties of other molecules and builds complex particles with a coordination number 4, as well as coordination number 6, via O-, but also via N-donor atom [3,26].

Biological role of manganese

Manganese is a weakly present element in biological systems, but also has an irreplaceable role in detoxification from oxygen free radicals as a cofactor of the enzymes catalase, peroxidase and superoxide dismutase. Manganese(II) is also an active center of the enzyme arginase which takes part in the cycle of urea as the final product of nitrogen metabolism [12].

The level of the presence of this metal in the human body is bound to the occurrence of oxidative stress, as free radical damage to mitochondrial DNA [30].

The Mn(II) ion of the d^5 electron configuration easily builds complexes with a coordination number 6, but are also only slightly stable and easily interact with other molecules, which leads to changes in the ligands and building of new products [3,26].

ANTI-INFLAMATORY DRUGS OF THE ACID TYPE

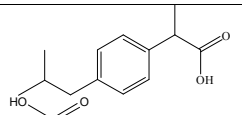
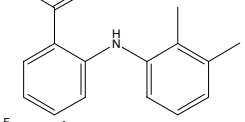
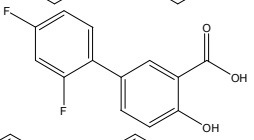
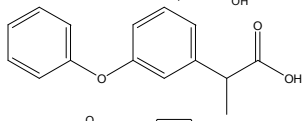
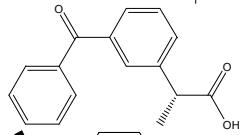
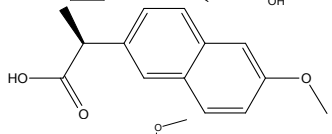
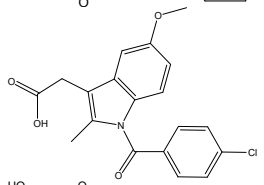
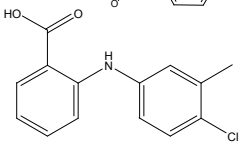
Anti-inflammatory drugs are a group of chemically varied substances which have analgesic, anti-pyretic and anti-inflammatory effects. Non-steroidal anti-inflammatory drugs (NSAIDs) of the acid type with a carboxyl functional group are made up of the following type of chemical class derivates: salicylic acid, phenylalkanoic acids, oxicams, anthranilic acids, sulphonamides and furanones. Some of the most widely used NSAIDs include ibuprofen, aspirin and paracetamol [20,31].

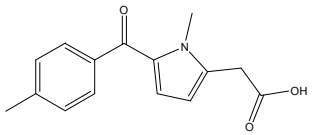
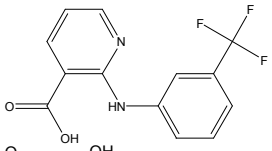
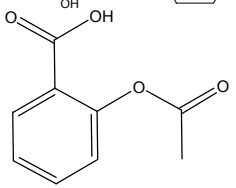
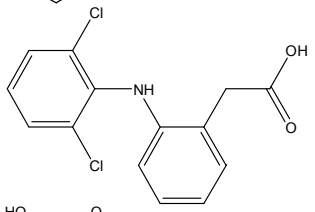
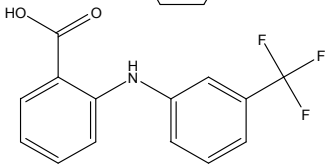
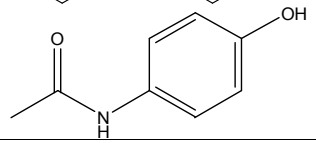
The anti-inflammatory activity of non-steroid anti-inflammatory drugs, as well as most of their other pharmacological activities, has to do with the inhibition of the conversion of arachidonic acid to prostaglandin which are the mediators of inflammatory processes [1]. Non-steroid anti-inflammatory drugs are potential inhibitors of cyclooxygenase *in vivo* and *in vitro*, significantly decrease the synthesis of prostaglandin, prostacyclin and thromboxane [32]. Non-steroid anti-inflammatory drugs of the acid type are shown in Table 2.

PRODUCTS OF INTERACTION BETWEEN M(II) METALS AND NSAIDs OF THE ACID TYPE

The coordination and structure of the complex associate, which originates as a result of interaction between M(II) metal ions and ligands (NSAID of the acid type), depend on the nature of the central metal ion (values of energy of ionization, completion of the d-sublevels, ion radius, and polarizability) and the nature of the ligand (electron charge, field-strength of the ligand, duration of the metal-ligand link). All of

Table 2: Non-steroidal anti-inflammatory drugs of the acid type

Generic name	IUPAC name	Formula	Application	References
Ibuprofen	(*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid		Acute and chronic pain, osteoarthritis, rheumatoid arthritis	[33,34]
Mefenamic acid	2-(2,3-dimethylphenyl)aminobenzoic acid		Pain, including menstrual pain, migraine headaches	[35]
Diflunisal	2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid		prostaglandin production inhibition, an anti-pyretic	[36]
Fenoprofen	2-(3-phenoxyphenyl)propanoic acid		rheumatoid arthritis, osteoarthritis, and mild to moderate pain	[37]
Ketoprofen	(*RS*)-2-(3-benzoylphenyl)propanoic acid		analgesic and anti-pyretic effects	[38]
Naproxen	(+)-(*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid		for relief of a wide variety of pain, fever, inflammations, stiffness	[39,40]
Indomethacin	2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid		To reduce fever, pain, stiffness, and swelling	[41,42]
Tolfenamic acid	2-[(3-chloro-2-methylphenyl)amino]benzoic acid)		analgesic, anti-inflammatory, anti-rheumatic, anti-pyretic effect	[43]

Tolmetin	[1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl]acetic acid		The regulation of hormones which affect the symptoms of swelling, pain, sensitivity, stiffness in the case of osteoarthritis and rheumatoid arthritis, as well as spondyloarthritis	[44]
Niflumic acid	2-{[3(trifluoromethyl)phenyl]amino} nicotinic acid		The treatment of inflammatory rheumatoid disorders	[45]
Aspirin	2-acetoxybenzoic acid		relieves minor aches and pains, reduces fever, an anti-inflammatory drug	[46]
Diclofenac	2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid		A cure for inflammatory processes, an analgesic and a cure for dysmenorrhea	[47]
Flufenamic acid	2-{[3-(Trifluoromethyl)phenyl]amino}benzoic acid		Anti-pyretic, analgesic and anti-inflammatory effect, used for skeletal-muscle disorders	[48]
Paracetamol	*N*-(4-hydroxyphenyl)ethanamide *N*-(4-hydroxyphenyl)acetamide		pain reliever, fever reducer, a slight anti-diuretic effect	[49]

these features of M(II) ion and ligand lead to different geometry of the complex ion which can be determined by spectroscopic studies and various analytical techniques, including the following:

UV/VIS spectrophotometry

This technique is suitable for determining the active substances in pharmaceuticals and biological samples. This technique offers data on the energy of the splitting of the d-energy sublevels, strength and type of the metal-ligand bond, geometric distribution of the donor atom of the ligand around the central metal ion, and symmetric characteristics of the complex [50-54].

IR/FTIR (Infra-red/Fourier transform infra-red)

This spectroscopic technique is used to obtain information on the type of coordination between metals and ligands, the denticity of the ligands, as well as the symmetry of the isolated products [55-57].

X-ray diffraction

This analytical technique is used to determine the structure of the studied compounds of the modelled isolated firm products [48,58-60].

ESR (Electron spin resonance spectroscopy)

This method is used to obtain data isolated from the products of the interaction between the paramagnetic M(II) metal ions and NSAID ligands on: the oxidation state of the metal, its coordination number, type of ligands, geometric structure and spatial distribution of the donor atom, the strength of the interaction between the metal and ligand [52,61-64].

ESI-MS (Electrospray ionisation mass spectrometry)

This technique can be used to detect the products of the interaction between metals and organic ligands in solutions at a micromolar level [65,66].

Useful information on coordination compounds of metal ions and NSAIDs can also be obtained using NMR [67,68], DTA and TGA [69,70] analyses. In order to determine the constants of stability, stoichiometric content, small amounts of metals and ligands, we also use AAS [4,71], cyclic voltammetry [39,72,73], potentiometric analyses [74], polarography [75], high-performance liquid chromatography (HPLC) [76], magnetic and molar conductivity measurements [47,77].

COMPLEXES OF M(II) BIOMETAL IONS AND NSAIDs

Carboxylate ligands, RCOOH, depending on the size and structure of the R remains, as well as the physical-chemical features of metal ions, behave like ligands of various dentate features, where the bonds are primarily enabled via the O-donor atom of the carboxylate anion (Figure 1). The denticity of the ligand was determined using the IR/FTIR specter on the basis of changes in the assignations of symmetrical and asymmetrical C=O vibrations $\Delta V = \nu_{asym}(C=O) - \nu_{sym}(C=O)$ of the carboxyl group [55-57]. The geometric structure of the isolated complexes were determined based on the characteristics bands on the UV/VIS spectrum [50-54], as well as changes registered by means of the X-ray diffraction analysis [58-60].

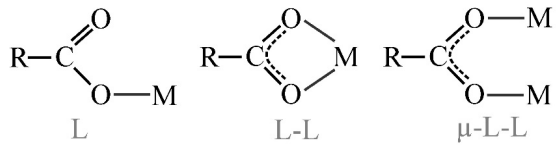


Figure 1: The type of coordination between the M(II) biometal ions and the –COOH group of NSAIDs

NSAIDs as monodentate RCOOH ligands

Not much can be found in the relevant literature on the complexes of the NSAIDs acid type and biometals of the $[ML_4]^{2-}$ type. In the reaction between ibuprofen and the Cu(II) ion [1] a compound was obtained, $[Cu(ibf)_4]^{2-}$, whose structure was determined using an elemental analysis, the NMR and UV/VIS technique. Ibuprofen also react, beside Cu(II) ion, with Co(II) ion via O-donor atoms of carboxylic group, as discussed by Nikolić *et al* [78].

Mefenamic acid builds complexes with the Co(II) ion as a monodentate ligand ($\Delta\nu$ = 224 - 230 cm^{-1}),defined as having an octahedron structure (three bands in the UV/VIS spectrum: 733 - 742 nm ($^2T_{1g}(F) \rightarrow {}^4T_{2g}$), 535 - 565 nm ($^4T_{2g}(F) \rightarrow {}^4A_{2g}$) and 440 - 475 nm ($^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$) which interacts with the DNA, the albumin serums, and indicates a significant antioxidative feature [72].In the presence of N,N-donor ligands, mefenamic acid builds a mixed compound with the Zn(II) ion, which has a distorted octahedral geometry $[Zn(mef)_2(Hpko)_2]$ and which displays anti-inflammatory activity, as well as a good affinity towards bonding with the CT DNA and the albumin serums. In this compound, mefenamic acid behaves as a monodentate ligand which is

indicated by the lack of a signal at 12.95 in the ^{1}H-NMR spectrum and Δν value above 190 cm^{-1} [77].

Naproxen builds a compound with the Co(II) ion (three bands in the UV/VIS spectrum: 735 - 740 nm ($^2T_{1g}(F) \rightarrow {}^4T_{2g}$), 535 - 570 nm ($^4T_{2g}(F) \rightarrow {}^4A_{2g}$) and 445 - 450 nm ($^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$) in the presence or absence of the N-donor heterocyclic ligands. The same type of behavior can be determined for the monodentate ligand (Δν = 204 - 216 cm^{-1}). The resulting complexes can interact with DNA, albumin serum, and have a significant antioxidative activity [39].

Niflumic acid as a monodentate ligand (Δν = 217 cm^{-1}),via the O-donor atom of the carboxyl group, builds a high-spin octahedral complexes with the Mn(II) ion, which easily participates with exchange reactions with ligands and builds compound associates with the DNA [45]. With this anti-pyretic, even the Co(II) ion builds complex octahedral structures which also take part in the exchange reactions with ligand and build compound associates with DNA and albumin serum [79]. The general formula of the built complexes of Co(II) and Mn(II) ions and niflumic acid is $[M(nifl)_2(MeOH)_4]$.

Tolfenamic acid and Co(II) build an octahedral complex (band in the UV/VIS: 680 - 720 nm ($^2T_{1g}(F) \rightarrow {}^4T_{2g}$), 540 - 565 nm ($^4T_{2g}(F) \rightarrow {}^4A_{2g}$) and 470 - 485 nm ($^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$) with the participation of solvent molecules in the first coordinating sphere $[M(RCOO)_2(L)_4]$, that is $[M(RCOO)_2(L\text{-}L)(L)_2]$. In this compound, which shows an affinity for the DNA and albumin serums, tolfenamic acid behaves like the monodentate ligand (Δν = 195 - 204 cm^{-1}) [22].

The complex of the octahedral structure which shows a great affinity to binding with the CT DNA also builds Cu(II) ion with diflunisal as a monodentate ligand (Δν = 201 - 208 cm^{-1}) [59].

Complexes of the type $[ML_4]$ of a square planar structure which manifest anti-cancer activity, SOD and catalase activity, COX inhibition, DNA binding properties and nuclease activity, are built by aspirin [80]. With Cu(II),the same compounds have a good tolerance among the studied patients and did not indicate any kind of unwanted effects [76]. The square-planar complex of Co(II) with aspirin have a good antibacterial response to *Bacillus substilis, Serratia species* and *Escherichia coli* [81]. The stability of the compound of various M(II) ions with aspirin decreases in the rank order: $Cu^{2+} > Co^{2+} > Zn^{2+}$ [74].

NSAIDs as bidentate RCOOH ligands

A far greater number of complex compounds of NSAIDs are built with bivalent ions of biometals as bidentate ligands (L–L). At the same time, they build mononuclear or polynuclear complexes, usually of a mixed type with a coordination number of metals of 4 or 6. Complexes of the type $[M(L–L)_2]$, $[M(L–L)L_4]$, $[M(L–L)_2L_2]$, $[M(L–L)_2(L'–L')]$ are built by almost all ligands of the acid type.

Mefenamic acid builds complexes with M(II) ions as a monodentate ligand [72,77] but can build mixed complexes with the Cu(II) ion as a bidentate ligand (Δν = ν_{asym}(C=O) – ν_{sym}(C=O) = 170 cm^{-1}) in the presence of N-donor heterocyclic ligands with a general formula of $[M(mef)_2(N,N\text{-})]$. The obtained octahedral compounds (UV/VIS bands in the region of 650 – 690 nm, which is ascribed to the $^2E_g \rightarrow {}^2T_{2g}$transfer) are tetragonally distorted and indicate a high antioxidative activity, as well as the affinity for DNA and albumin serum [35]. A complex of similar pharmaceutical and geometric characteristics of mefenamic acid as a bidentate ligand is built by Zn(II) ion in the presence of the N-donor ligand bipyridyl [77].

The Cu(II) ion with naproxen and diclofenac as bidentate ligands in the presence of N,N-donor ligands builds compounds which have good anti-tumor and anti-microbial activity[73].

Complex compound of the Zn(II) ion with naproxen with the aim of decreasing the anti-ulcer effect of this NSAID was synthesized. The obtained complex with naproxen as a bidentate ligand (IR: Δν = 150 cm^{-1}; ^{13}C NMR: a shift in absorption of –COOH from 177,66 to 179,79 ppm) showed a significant reduction in ulcers as compared to that of naproxen and a physical mixture of naproxen [77].

Ibuprofen, as a bidentate ligand, builds complexes with the Cu(II) and Zn(II) ion in the presence of solvent molecules or N,N-donor ligands. The value of Δν is 160 - 170 cm^{-1} for the complex with the Cu(II) ion [82], that is 130 - 140 for the complexes with the Zn(II) ion, where the TGA analysis determined the presence of an H_2O molecule in the internal coordination sphere $[Zn(ibf)_2(H_2O)_2]$. The compounds obtained with Zn(II) indicate good antibacterial activity and cell culture and growth inhibitory activity [4,32].

In the presence of the N-donor ligand imidazolefenoprofen behaves as a bidentateO-donor (Δν = 187 cm^{-1}) ligand and builds an octahedral complex (λ_{max} = 660 nm) with the

Cu(II) ion [$Cu(fen)_2(im)_2$], which has significant SOD mimetic activities and moderate catalytic oxidase activity[83]. Complexes with a square-planar structure (λ_{max} = 580 nm) are built by ketoprofen with Cu(II) which has a significant anti-proliferative activity, while ketoprofen behaves as a bidentate ligand [84].

Tolfenamic acid builds octahedral complex with Co(II) ion, where it behaves as a bidentate ligand], ($\Delta\nu$ = 171 cm^{-1}). The built complex indicates a greater affinity for DNA and albumin serum binding, compared to the complex with mefenamic acid [28].

All the complex NSAIDs with biometals indicate a better pharmacological activity than the NSAIDs themselves [4,28,32,37,71].

NSAIDs as O-donor ligands in polynuclear compounds

The carboxylate anion in pharmaceuticals such as NSAIDs easily builds polynuclear complexes with small ions of M(II) metals, in which the bridging ligands (μ-L~L) lie between two M–M centers. The greatest numbers of these compounds are built with copper. Binuclear complexes that are built by Cu(II) ion in coordination with O-donor ligands, namely, fenoprofen, tetracarboxylates, indomethacin, ibuprofen and ketoprofen indicate improved anti-inflammatory effects [41,64]. Using IR/FTIR technique, the denticity of the ligands was determined, while the value of $\Delta\nu$ as well as the type of chelate complexes of Cu(II) ions with NSAIDs are shown in Table 3.

Table 3: Binuclear Cu(II)-NSAIDs complexes and the corresponding $\Delta\nu$ values of the carboxyl group

NSAIDs	Complex	$\Delta\nu$ [cm^{-1}]	Ref.
Mefenamic acid	$[Cu_2(mef)_2(H_2O)_2]$	170	[35]
Fenoprofen	$[Cu_2(fen)_2(DMF)_2]$	206	[37]
	$[Cu_2(fen)_2(caf)_2]$	193	[83]
Diflunisal	$[Cu_2(difl)_2(dmf)_2]$	185	[59]
Ibuprofen	$[Cu_2(ibf)_2(H_2O)_2]$	172	[70]
Naproxen	$[Cu_2(naprox)_2(H_2O)_2]$	201	
Tolmetin	$[Cu_2(tolm)_2(H_2O)_2]$	184	
Diclofenac	$[Cu_2(dicl)_2(H_2O)_2]$	184	
Tolfenamic acid	$[Cu_2(tolf)_2L_2]$	145	[58]

The internuclear distance between Cu(II)-Cu(II) centers in the built complexes, based on the results of the X-ray analysis, ranges in interval from 2.6075 Å for tolfenamic acid [58] to 2.661 Å in the case of diflunisal [59].

These binuclear complexes of the Cu(II) have a better anti-inflammatory activity than the pure drug [37,41], good affinity for DNA and albumin serum binding [35,59], catechol oxidase mimetic activity [37], SOD mimetic activities [58,83], inhibition of polymorphonuclear leukocyte oxidative metabolism [60].

Ibuprofen, ketoprofen and naproxen with the Cu(II) ion also build binuclear complexes, and their existence in the physiological conditions was determined using the ESI-MS technique [85]. Cu(II) ion also builds binuclear complexes with aspirin [$Cu_2(asp)_4$], and shows the same anti-thrombotic activity and inhibits the platelet-neutrophil interaction [86], as the improved anti-inflammatory effect of aspirin itself [88]. This group of authors determined the existence of bidentate associates on the bases of the peak which was determined in the ESI-MS specter of the studied Cu-asp system at 848.10 *m/z*). Interaction of M(II) metal ions on micromolar level was studied by ESI-MS LOOP-chromatogram method Area under peaks on LOOP-chromatograms in presence of Cu(II), Co(II), Cd(II)-ions is smaller than the corresponding area for ibuprofen without metal ions which shows that there is a significant interaction M(II)-IB at micromolar level and that the interaction is the most expressed in Co(II)-IB system [88].

M(II) Biometal ions complexes with the NSAIDs derivative, paracetamol

In terms of use, of all the NSAIDs, paracetamol (PA) holds the first three positions. Relevant literature contains data on the study of the interaction between M(II) metal ions and the NSAIDs derivative of carboxylic acids, PA [74,89]. Using CNDO calculations of electronic energy showed that the isolated compounds of M(II) ions of the studied metals (Cu and Zn) along with PA belong to the C_{2h} point group symmetry. On the basis of spectroscopic data, the obtained UV/VIS, IR and ^{1}H-NMR, this group of authors considers the studied M(II) ions to build complex quadrangle-planar structures with PA via the N- and O-donor atoms, with a metal-ligand = 1:2 ratio. [89] UV/VIS spectral data of paracetamol complex with Co(II) and Cu(II) ions in molar ratio M:L = 1:2. (λ_{max} = 593 nm, ε = 2.95 × 10^4 for Cu-PA and λ_{max} = 574 nm, ε = 0.7 × 10^3 for Co-PA) indicate the participation of -NH-group of paracetamol in complex formation because λ_{max} for complexes with only O-donor ligands have much higher values. IR spectral data for the same complexes (M-N at 520 - 530 cm^{-1} and M-O at 600 - 610 cm^{-1}, and retention of the strong band corresponding to the stretching

vibration of O-H group) indicate that phenolic -O-H group of paracetamol was not directly involved in the complex formation [90].

Polygraphic method showed that the complex originated between the Zn(II) ions and paracetamol with a stoichiometric composition of M:L = 1:1, where the paracetamol behaves as a bidentate O-donor ligand. The obtained compound exhibits good analgesic activity, better than the pure form of the drug [75]. Co(II)-alkyne complexes derived from acetylsalicylic acid represent a new group of organometallic cytostatics, where the inhibition of the COX plays the main role [91].

CONCLUSION

Biometals achieve interaction with acid-type anti-inflammatory drugs at micromolar and millimolar levels. R-COOH behaves as monodentate, bidentate or a bridge ligand, which can be reliably determined based ona model system, where in the complexes are formed with different stoichiometric compositions, and the geometric structures, which can be determined using various analytical techniques (UV/VIS, FTIR, EPR, X-ray, ESI-MS, etc.). The associates obtained are important for the following reasons: theory of coordination chemistry, significance of the development of new methods for determining micro amounts of active components, to achieve more balanced therapeutic dosing, biodistribution of medicine, monitoring its pharmacokinetics including excretion; reduction of unwanted responses, improvement of anti-microbial activity, synergistic effect of the metals and medicine, as well as improved anti-ulcerous, anti-tumor and anti-bacterial activity.

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