Coordination Chemistry Reviews 253 (2009) 2588–2598

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Biological activity of metal ions complexes of chromones, coumarins and flavones

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Contents

ARTICLE INFO

Article history:
Received 15 January 2009
Accepted 20 June 2009
Available online 26 June 2009

Keywords:
Chromone
Coumarin
Flavonoid
Metal complex
Disease

ABSTRACT

The medical properties of naturally occurring compounds such as chromones, flavonoids and coumarins have been well known for many years. However, the discovery that their complexes with metal ions are more effective than coumarins and flavonoids alone changed the course of drug research. Numerous studies showed that these complexes can be successfully used in a range of diseases such as diabetes mellitus, some bacterial infections or even cancers. In this account their role in the treatment of neurodegenerative diseases, like Huntington's disease, or in preventing conditions like heavy metal poisoning is discussed. The complexes can also influence the equilibrium of iron within a living organism, which is an important factor in the treatment of diseases like Friedreich ataxia and β-thalassemia.

Abbreviations: EGCG, polyphenol (−)-epigallocatechin-3-gallate; IC_{50}, the 50% inhibitory concentration; MNC, maximal nontoxic concentration; PET, photoinduction of electron transfer; SF34, fluorescein labeled iron(III)-sensitive sensor; Akt/PKB, serine/threonine kinase; AML, acute myelogenous leukemia (AML); A549, lung cancer cells; B16F10, melanoma cell line; BAX, gene; *cis*-DDP, *cis*-diamminedichloroplatinum(II); DM KKA^{y}, the KKAy mouse, a rodent model of non-insulin-dependent diabetes mellitus; EDTA, ethylenediaminetetraacetic acid; FFA, free fatty acid; GLUT4, insulin-regulated glucose transporter; HSL, skeletal muscle hormone-sensitive lipase; HCCA, coumarin-3-carboxilic acid; HIV-1, human immunodeficiency virus type 1; HL-60, *human promyelocytic leukemia cells*; huntingtin, HD protein; K562, human leukemia cell line; L1210, mouse lymphocytic leukemia cell line; MCF-7, human, Caucasian, breast, adenocarcinoma; monHER, 7-monohydroxyethylrutoside; MPTP, methacryltriisopropoxytitanium mouse model; NALM-6, human, peripheral blood, leukemia, pre-B cell; PA, pyrazoloacridine; PD, Parkinson's disease; P3HR1, EBV-positive Burkitt's lymphoma cell line, EBNA2 deletion; PKA, cyclic AMP-dependent protein kinase A; ROS, reactive oxygen species; SCLC, small-cell lung cancer; SRS, superoxide radical scavenging; THP-1, Human acute monocytic leukemia cell line; 3T3 cells, the standard fibroblast cell line; T98G, human, Caucasian, glioblastoma; WD, Wilson disease; Xiao-Chaihu-tang (Sho-saiko-to), hepatoprotective Chinese traditional herb medicine mixture; MIC, minimal inhibitory concentration.

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doi:10.1016/j.ccr.2009.06.015

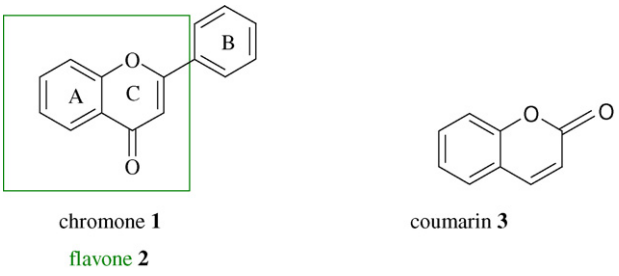

Fig. 1. The structure of chromone (4*H*-benzopyran-4-one) (**1**), flavone (2-phenyl-1,4-benzopyrone) (**2**) and coumarin (1,2-benzopyrone) (**3**).

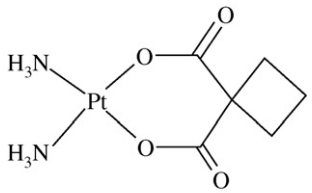

Fig. 2. The structure of carboplatin (*cis*-diamine(1,1-cyclobutanedicarboxylate)-platinum(II)) (**4**).

1. Introduction

Around the world scientists try to design successful cures against still incurable diseases such as AIDS, diabetes or some cancers. It has been known for many years that metal ions such as copper(II), iron(II), iron(III) or platinum(II) exert wide biological activity, for example against tumor cells. Also chromones (**1**, Fig. 1), flavonoids (**2**, Fig. 1) and coumarins (**3**, Fig. 1) have been known for similar properties. These two facts prompted scientists to check whether complexes of those metals and ligands would be more active than the basic compounds. The biological activity of some of these complexes recently described in the literature, is similar to that of widely used carboplatin {cisdiamine(1,1-cyclobutanedicarboxylate)-platinum(II)} (**4**, Fig. 2) [1–6]. Here we would like to present selected complexes of the aforementioned compounds and examples of their use in the treatment of some illnesses.

2. Chromones, flavonoids, coumarins and metals and their abilities

In recent years, due to increasing public interest in healthy lifestyles and disease prevention and treatment, dietary supplements and cures containing high doses of chromones (4*H*-benzopyran-4-one) (**1**, Fig. 1), flavonoids (2-phenyl-1,4-benzopyrone) (**2**, Fig. 1) or coumarins (1,2-benzopyrone) (**3**, Fig. 1) have became very popular [7].

Flavonoids-related chromone (**1**, Fig. 1) and its derivatives are well known naturally occurring heterocyclic compounds with oxygen as a heteroatom [8]. They have antibacterial, antifungal, anticancer, anti-HIV, spasmolytic and antiviral properties [9,10]. To date, only one alkaloid-related chromone – noreugenin has been found [8]. Hormothamnione (**5**, Fig. 3) and 6-desmethoxyhormothamnione (**6**, Fig. 3), which are styrylchromones from the marine crytophyte *Chrysophaeum taylori*; possess antitumor activity against lymphocytic leukemia and HL-60 promyelocytic leukemia cell lines *in vitro*. Compound **6** is also cytotoxic towards 9 KB cell lines. However, isolation of those chromone derivatives is quite problematic, because they are present at really low concentration in rare algae [11,12].

Coumarin (**3**, Fig. 1), the basic molecule of the family of many derivatives, is the simplest naturally occurring phenolic substance possessing fused benzene and α-pyrone rings. The coumarins exist in a variety of forms, due to the various substitutions possible in their basic structure, which modulate their biological activity [13,14]. Coumarins possess anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, antithrombotic, antiviral, antimicrobial and anti-carcinogenic properties. Moreover, the function of plant growth hormones and growth regulators depends on them, as well as the control of respiration, photosynthesis and defense against infection [15,16]. Evolution developed a very long association of plant coumarins with other organisms which may account for the extraordinary range of their biochemical and pharmacological activities in mammals and other biological systems. The hydroxycoumarins are phenolic compounds able to act as potent metal chelators and free radical scavengers [17]. Some coumarins can be obtained from chromone derivatives. Starting from 2-methyl-4-oxo-chromone-3-carboxylic acid (**7**) we formed new coumarin derivatives 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione (**8**, Fig. 4) which display cytotoxic activity against HL-60, NALM-6 cell lines [18]. Also, we converted 2-methyl-4-oxo-4*H*-chromone-3-carboxylate (into new coumarin derivatives (**9**, Fig. 5) which possess low activity against A549, K562 and HeLa cells [5].

Flavonoids (*flavus* – yellow) (**2**, Fig. 1) form a ubiquitous group of polyphenolic substances typically produced by plants. They are present mainly in seeds, fruit skin, peel, bark or flowers and exert antibacterial, anti-inflammatory, anti-allergic, anti-mutagenic, anti-viral, anti-neoplastic, anti-thrombotic [19]. Flavonoids are present in plants either as aglycones or as glycoside conjugates, and are involved in plants' growth, reproduction and resistance against pathogens and predators [20,21]. Bound sugar moieties include D-glucose, L-rhamnose, glucorhamnose, galactose, lignin, and arabinose. They are able to interact with many drugs through the inhibition of P-glycoprotein and/or drug-metabolizing enzymes but the process could be mediated also by other major efflux drug transporters [22]. Because of struc-

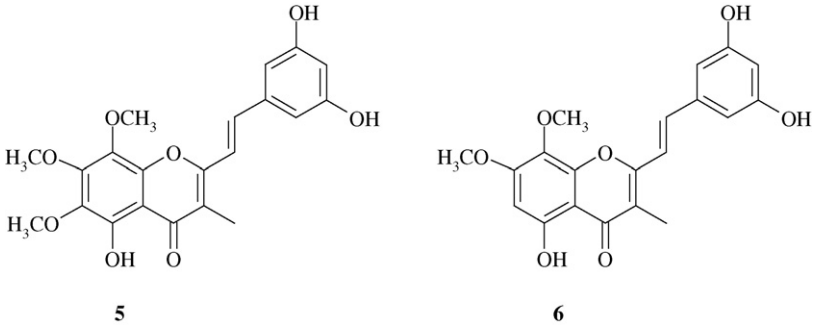

Fig. 3. The structure of hormothamnione (**5**) and 6-desmethoxyhormothamnione (**6**).

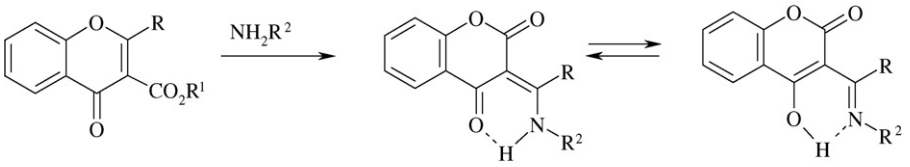

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Fig. 4. The structure of coumarin derivatives obtained from [1-(alkyloamino)-ethylidene]-chroman-2,4-dione (**8**) [18].

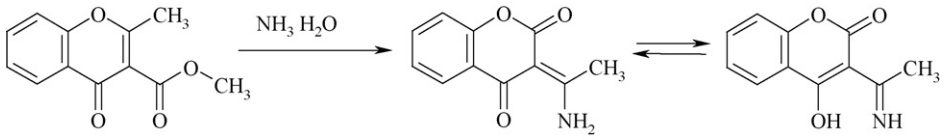

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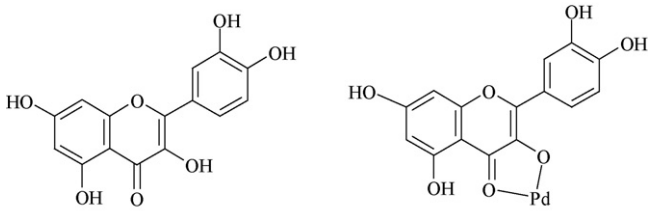
Fig. 5. Synthesis of coumarin derivatives from 2-methyl-4-oxo-4*H*-chromone-3-carboxylate (**9**) [5].



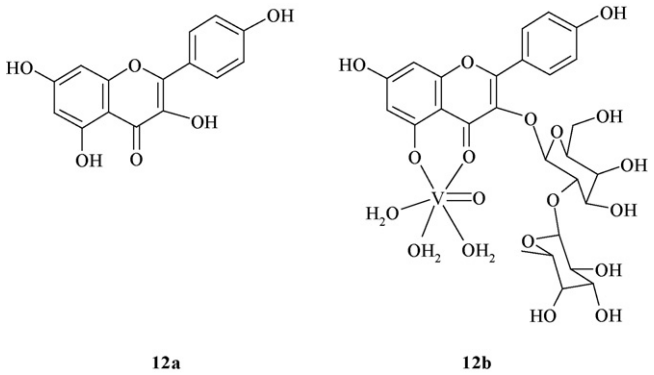
10a 10b

Fig. 6. The structure of quercetin (**10a**) and Pd(II)-quercetin complex (**10b**).

tural differences flavonoids are divided into eight different groups: flavonols {quercetin (**10a**, Fig. 6), myricetin (**11**), kaempferol (**12a**, Fig. 7), and rutin (**13**)}, flavanones {taxifolin (**14**)}, flavones {luteolin (**15**) and apigenin (**16**)}, isoflavones {daidzein (**17**) and genistein (**18**)}, catechins, anthocyanidins, dihydroflavonols and chalcones [23]. Biological activity of these small molecules often depends on their complexes with proteins; the formation of which is affected by their three-dimensional structure and electrostatic interactions. Areas of highest electronegativity tend to appear at the 5-hydroxyl and 7-hydroxyl positions of the A-ring, at the various hydroxylations of the B-ring, and at the 3-hydroxyl position of the C-ring – specific to flavonols [17,24].

Flavonoids can be effective drugs for neuronal diseases because of their potent iron-chelating, radical-scavenging, anti-inflammatory and neuroprotective properties [25,26]. For example epigallocatechin-3-gallate (EGCG) (**19**, Fig. 8), a polyphenol which is present in the green tea extract, is not only an excellent antioxidant and metal (iron and copper ions)-chelator but also possesses access into the brain which is really important in neuronal treatment [25]. EGCG seems to be a good remedy for neuronal diseases due to the 3′,4′-dihydroxyl group in the B ring, as well as the gallate group, which may neutralize ferric iron to form redox-inactive iron, thereby protecting cells against oxidative damage [27]. In a MPTP mouse model (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine *mouse model*) compound **19** can also protect the brain preventing Ab-induced neurotoxicity [28]. The discovery that metal ions perform structural and catalytic functions in association with proteins and enzymes, opened new directions in research [29]. Metal ions are crucial to the proper functioning of all living cells, and any disruption can lead to serious neuropsychiatric diseases such as Alzheimer's, Menkes', Wilson's and Parkinson's diseases, Friedreich's ataxia and Hallervorden–Spatz syndrome [30].

Metal ions which possess redox activity act as cofactors for various enzymes, but they are also cytotoxic as they generate reactive oxygen species [31]. For example, copper(II) is a cofactor for numerous enzymes (e.g. cytochrome oxidase, superoxide dismutase, dopamine-hydroxylase) [32] and is involved in redox activity and in catalysis. Nonetheless, it is also toxic and its use has to be restricted to avoid exacerbating oxidative stress and damage connected with aging and disease [30]. For instance, its binding to sulfhydryl groups of the amyloid precursor protein suggests involvement in development of Alzheimer's disease [33]. Furthermore, the prion protein binds and internalizes copper into brain cells. Therefore, an incorrect copper balance could be a cause of human Creutzfeld-Jacob's disease, or bovine spongiform encephalopathy [34,35]. Similarly, zinc is an essential nutrient required to sustain all forms of life,



12a 12b

Fig. 7. Possible structure of the kaempferol (**12a**) kaempferol-3-neohesperidoside VO(IV) complex (at physiological pH) (**12b**).

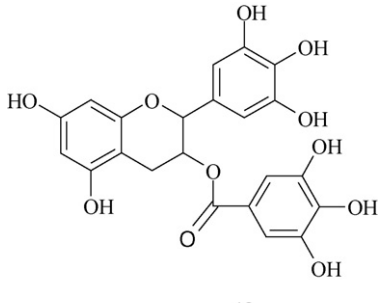


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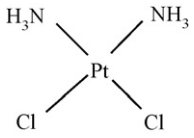
Fig. 8. The structure of polyphenol (−)-epigallocatechin-3-gallate (EGCG) (**19**).



20

Fig. 9. The structure of the most popular platinum forms: cisplatin (*cis*-diamine-dichloroplatinum) (**20**).

2–3 g of it are necessary for proper function of human organisms [30].

Iron ions exist in two forms ferrous Fe(II) or ferric Fe(III). In organisms iron ions are tightly bound by enzymes and storage transporter proteins. As with zinc(II) and copper(II), unregulated iron ions concentration can lead to undesired oxidative reactions [30]. It is noteworthy that iron ions also possess antitumor activity as they induce apoptosis upon complexation with nucleosides or with pentadentate pyridyl ligands. Furthermore, iron ions are necessary to hemoglobin synthesis, DNA synthesis, and electron transport [36]. Iron ions are also involved in the peroxidation of the mitochondrial membrane lipids, a process which is connected with the impairment of membrane-dependent functions of mitochondria and lysosomes [37].

A common cytotoxic metal complex is *cis*-diamine-dichloroplatinum (cisplatin) (**20**, Fig. 9) which possesses activity against several human malignant diseases, such as: lung, bladder, neck and head, ovarian cancers. Although it is widely used around the world, it causes serious side effects such as gastrointestinal and hematological toxicity. The cytotoxic activity of compound **20** may be a consequence of its binding to DNA (more precisely to guanine(s) at N7 sites giving several types of DNA adducts: monoadducts, interstrand crosslinks, intrastrand crosslinks and DNA-protein crosslinks) [38].

Carboplatin (**4**, Fig. 2) possesses a cyclobutanedicarboxylate group which, like cisplatin, can react with glutathione and metallothioneins. It reacts with a ligand by ring opening after loss of the malonate ligand. Compound **4** possesses lower cytotoxic activity in numerous cell lines such as head and neck cancers, and bladder or esophageal carcinomas. However, in other cell lines (ovarian cancer, extensive lung cancers) the activity is comparable to that of compound **20**. Other complexes of platinum like oxaliplatin (**21**), nedaplatin (**22**), lobaplatin (**23**), heptaplatin (**24**) can be isolated but only compound **21** and carboplatin (**4**) are commonly used while compound **22**, **23**, **24** (SKI2053R) are registered only in Japan, China, and South Korea [39–41].

3. Flavonoid–metal complexes

Flavonoids are effective metal ion chelators and play a key role in the initiation of free radical processes (*via* the Fenton reaction). Metal chelation is thought to be another mechanism of flavonoids antioxidant activity, which, along with some biological effects of flavonoids, can be altered by flavonoid–metal interaction [42]. Flavonoids easily chelate metal ions and create complex compounds. Their additional antioxidant activity results from binding of metal ions like Fe(II), Fe(III) and Cu(I), which participate in free radical-generating reactions. Therefore, they act on two antioxidant pathways: (1) direct reactions with free radicals, (2) chelating of metal ions involved in production of reactive oxygen species [43–46]. Experimental data indicate that the chelated compounds are more effective free radical scavengers than flavonoids alone. For example, complexes of rutin (**13**), dihydroquercetin (**25**) or epicatechin (**26**) with Fe(II), Fe(III), Cu(II) or Zn(II) are more effective radical scavengers than the corresponding free flavonoids due to the acquisition of additional superoxide dismutating centers. The antioxidative activities of complexes of morin (1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside) – xanthone derivative (**27**) and Pd(II)- and Pt(II)-(**28**, Fig. 10) are greater than that of **27** itself. Moreover, the Pt(II)-complex has a stronger scavenging effect than the Pd(II)-complex. Both complexes inhibit lipid peroxidation to a greater extent than free compound **27** alone [47]. Some metal(III) complexes with quercetin affect DNA transcription and repress growth of tumor cells.

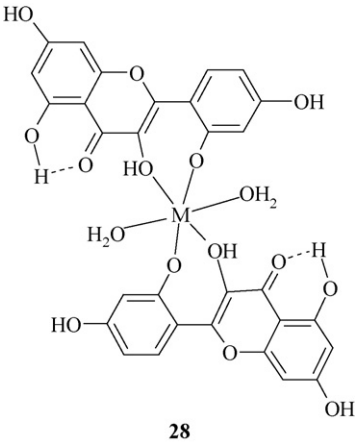


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Fig. 10. The structure of M(II)–morin (3,5,7,2′,4′-pentahydroxy-flavone) complex, where M is Pd(II), Zn(II) (**28**).

In 1962 the first complex of flavonoids with aluminum as a central ion was obtained. Since the early 1980s scientists have investigated about 40 metal–flavonoid complexes. The complexation causes a bathochromic shift in both I and II absorption bands. Similar shift has been noticed in all classes of flavonoids which have 5-hydroxy-4-keto, 3-hydroxy-4-keto and/or *o*-dihydroxy groups, suggesting that these kinds of substituents are important for chelation [46].

All types of flavonoids possess three domains able to react with metal ions: the 3′,4′-dihydroxy system located on the B ring, the 3-hydroxy or 5-hydroxy groups and the 4-carbonyl group in the C ring. The 3- or 5-hydroxypyran-4-one (sometimes the *ortho*-hydroxyl) groups in the B flavonoid ring play a principal role in chelating [43]. So far it is not clear which element of the ligand plays a key role in metal ion chelating.

Through IR spectroscopy of the Pd(II)–quercetin (**10b**, Fig. 6) and UO_2–rutin complexes, Malešev and Kunti [46] showed that the benzoyl moiety is the basic site for metal chelation. Cornard and Merlin [48] proved that the ortho-dihydroxyl system of quercetin (**10a**) is unable to bind Al(III) in acidic media. However, they indicated that the Al(III)–quercetin complexes possess two binding sides: 3-hydroxychromone, by which the complex is formed, and the *ortho*-hydroxy groups, which are active depending on the medium and pH.

For steric reasons the complexes usually include no more than two flavonoid molecules. However Zhou and co-workers through fluorescence spectroscopy found 3:1 complexes of quercetin (**10a**) with eight rare-earth metal ions [49].

Flavonoids act as weak polybasic acids, so pH plays an important role in complex formation. The optimal pH for complex formation is around 6, although it strongly depends on the metal ion. At pH below 3.0, flavonoids remain undissociated, which is unfavourable for complex formation. At high pH values flavonoids are deprotonated and form more complex species. Furthermore, at higher pH values metal ions cause side reactions (hydrolysis) and hydroxo-complexes are formed [46].

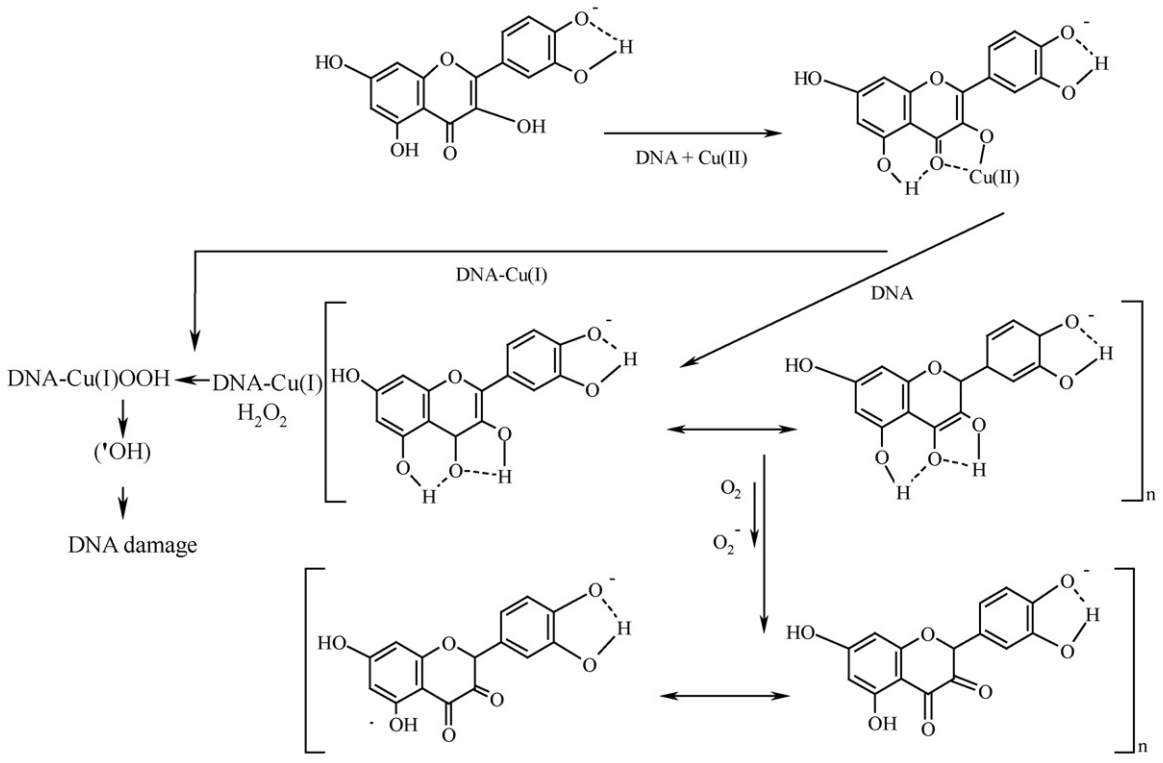

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Fig. 11. A probable mechanism of DNA damage induced by quercetin in the environment of Cu(II) (**29**) [50].

In highly stable complexes, the central ion is usually an anion, for example in complexes with rutin, morin or 3-hydroxyflavone the anion is WO_4^{2-} and ligand–metal interactions are partly electrostatic [46].

Three types of metal cytotoxicity were classified through studies of the Balb/3T3 cell line. Group I causes no cytotoxic effect or only a slight one and includes 26 species, group II exhibits remarkable cytotoxicity (13 metals) and group III induces strong cytotoxic response (19 metals) [14].

Quercetin (**10a**) can induce oxidative DNA damage in the presence of Cu(II) (**29**, Fig. 11). Similar ability is also presented by kaempferol (**12a**) and luteolin (**15**) but their activity is rather low. Probably only compound **10a** can effectively reduce Cu(II) to Cu(I), which is proposed to serve physiological function to maintain DNA structure, however it does not damage DNA directly. An important point is that while quercetin intercalates into DNA, the complex quercetin–Cu(II) (**30**) does not, and the complex DNA–Cu(I) responsible for DNA damage does not form. Quercetin (**10a**) has both mutagenic and carcinogenic effect, kaempferol (**12a**) possesses only mutagenic activity, while it looks that luteolin is neither mutagenic nor carcinogenic. Compound **12a** and luteolin (**15**) induce little DNA damage suggesting a relationship between carcinogenicity and the potential to damage DNA through oxidation [50].

4. Flavonoids– and coumarin–metal complexes as aid in treatment of incurable diseases

4.1. HIV and human cytomegalovirus

The best-known lentivirus is Human Immunodeficiency Virus, type 1 (HIV-1) which is an etiologic agent of AIDS. Its genome includes three structural and six regulatory genes encoding structural viral proteins and six unique regulatory/accessory proteins which play a critical role in HIV-1 gene expression, transmission, and pathogenesis [48,51].

It is assumed that an effective anti-HIV agent should inhibit HIV-1 replication. However, the HIV virus' structure requires any novel anti-HIV remedy to have a novel structure and/or new action mechanisms. Coumarins have been proposed as promising anti-HIV agents [52,53] because a large group of structurally novel coumarins act as non-nucleoside reverse transcriptase (RT) inhibitors [54] and demonstrate anti-HIV and anti-human cytomegalovirus activity. 4-Hydroxycoumarin (4-hc) residues, along with various other HIV-1 protease inhibitors, also demonstrate anti-viral, anti-protease and anti-integrase activities. Lanthanides: cerium Ce(III), lanthanum La(III), and neodymium Nd(III) are able to create complexes with coumarins ability. However, it is noteworthy, that the La(III)–warfarin complexes possess higher anti-HIV activity than warfarin (4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one) (**31**, Fig. 12) alone, but the Nd–warfarin complex has limited anti-HIV potency and is not used in clinical research.

3,3′-Benzylidene-bis(4-hydroxycoumarin) (**32**, Fig. 13) complexed with Nd displays at least five times lower cytotoxicity than

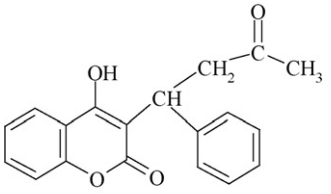

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Fig. 12. The structure of warfarin (**31**).

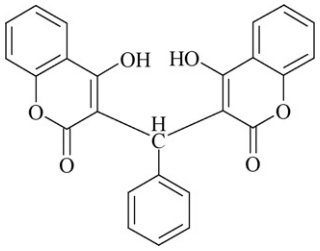


Fig. 13. The structure of 3,3′-benzylidenbis[4-hydroxycoumarin] (**32**).

when complexed with other lanthanides or in a metal-free form. Although the ligand MNC (maximal nontoxic concentration) value for different complexes could not be expected to be the same, surprisingly, Nd(I) and Ce(I) were maximally non-toxic at concentrations 10–50 times higher than La(I) and the ligand **31**. On the other hand, the ligand **31** and its complexes possess equal cytotoxicity and equal MNCs. Interestingly, using microtiter infection assay with HIV-1 infected MT-2 cells, the effect of ligands and their metal-complexes on HIV replication depends on the doses. Experiments with the use of **31** and **32** proved that, in all cases, the inhibitory effects in MT-2/HIV-1 system at or below the MNC values were low, and only the La-(II) complex was truly active (58.4%) against the virus. However, other experiments have shown that these complexes were not able to impair HIV double-stranded (ds) proviral DNA synthesis. Therefore, if neither the ligands nor their rare metal ion complexes have any effect on the reverse transcription, the active La(II) and the other less potent anti-HIV agents will not be active at the early stages of HIV replication. La(II) complexes were unable to affect the late stages of HIV-1 replication in cell culture [55,56].

4.2. Wilson's disease and Menkes' disease

Some coumarins can be used as fluorescent markers to detect and monitor the Cu(II) level, which can be useful in the detection of various diseases related to iron overload, like Menkes' or Wilson's disease (WD).

People with Menkes' disease suffer from huge problems in brain development and finally die due to neurodegeneration. In this genetic disease caused by copper transport disorders, the metal accumulates in the intestines, the kidneys, and in the cultured fibroblasts of the patients. One method of controlling the copper concentration within cells is chemical complexation. *In vivo*, this strategy has been utilized in the therapy of diseases associated with copper homeostasis. Parenteral administration of copper-histidine has some effect in the treatment of Menkes' disease, provided it is initiated before the occurrence of irreparable neurodegeneration [57].

Patients with WD also demonstrate a copper metabolism disorder – copper is accumulated in various tissues such as the liver, the kidney, the brain, and the placenta due to lack of biliary excretion of copper from the body [58]. Therefore, patients with WD have high levels of copper in the liver. The level of Cu(II) can be measured by photoinduction of electron transfer (PET), where it is possible to detect the presence of a Cu(II) chemosensor through the binding of a special chelator to diazotizated coumarin.

The fluorescent intensity of Cu(II)-**33** complex (where **33** is a compound based on a coumarin moiety) (**33**, Fig. 14) is nine times higher than that of **33** alone. Because Zn(II) and Mg(II) can be present at concentrations similar to Cu(II), it is important to have a fluorochrome specifically detecting Cu(II) [59]. The novel fluorescein labeled iron(III)-sensitive sensor SF34 features a 3-hydroxypyridin-4-one (HPO) chelation unit, which can bind to iron(III) with high affinity and selectivity.

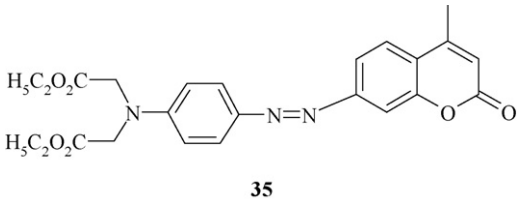


Fig. 14. The structure of compound which come from aniline (with coumarin moiety) complex (**33**).

In vitro, the fluorescent sensors are able to influence intracellular iron concentrations and the iron chelation potency. The organelle-specific fluorescent iron sensors are vital in research for an effective drug against iron overload disease [60].

4.3. Cancer

4.3.1. Leukemia cancer

Creating metal complexes as anticancer drugs is really promising but not easy because the accumulation of metal ions in the body can cause undesirable effects. Therefore, research for potential drugs should be carried out by *in vitro* study with targeted biomolecules and tissues as well as by *in vivo* investigation before they enter clinical trials. As the main aim of chemotherapy is the destruction of tumor cells without any undue influence on proper cells, it should not be forgotten that although metals cause desirable effects like cell division, they are also potentially carcinogenic [14].

Cisplatin (**20**) carboplatin's (**4**) antitumor activity is widely used in oncotherapy [61]. Carboplatin demonstrates a slower rate of conversion to reactive species than cisplatin [62] and it is able to open its ring, allowing it to bind to DNA [63]. Interestingly, replacement of the chloride group in cisplatin molecule with cyclobutanedicarboxylate ligand significantly diminishes the nephrotoxic effects of the carboplatin formed, without affecting its antitumor potency [64]. Cisplatin complexed with two large aminoflavone substituents in place of its ammonia groups is able to induce DNA damage, not only in a cell-free system but also in L1210 cells [65].

cis-Pt(II) complex of 3-aminoflavone (**34b**, Fig. 15), a synthetic bioligand which contains both *O*-atom (carbonyl) and *N*-atom (amine) sites to form chelate complexes, causes cell necrosis and apoptosis. This complex is able to inhibit deoxyribose degradation in the presence of Fe(II) ions. Importantly, it has a toxic effect on cancer cells such as leukemia L1210 cells in mice, while is much less toxic to normal cells. The main mechanism of this process is probably the induction of DNA breakage [66].

Lanthanides(III) are trace elements and their role is not well known yet. Kostova et al. [67] tested the anti-leukemia activity of lanthanide–coumarin complexes. They discovered that complexes of samarium(III), gadolinium(III), and dysprosium(III) with coumarin-3-carboxylic acid (HCCA) (**35**, Fig. 16) play a concentration-dependent anti-proliferative role towards the chronic myeloid leukemia-derived K-562 line [2].

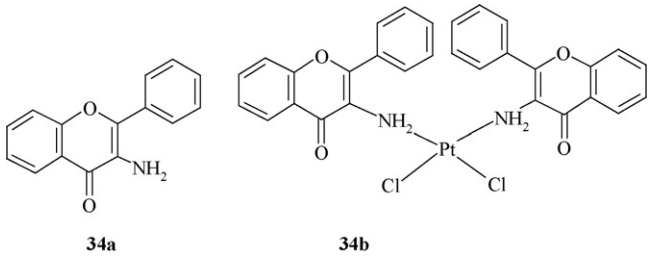
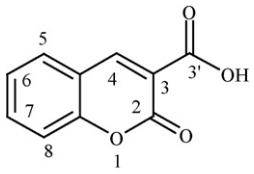
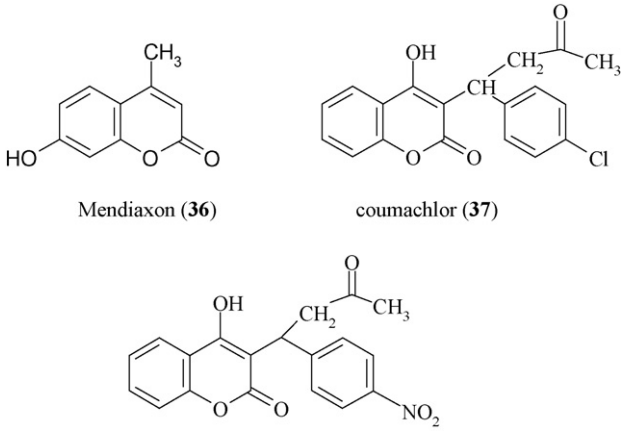


Fig. 15. The structure of 3-aminoflavone (**34a**) and complex with Pt(II) (**34b**).



35

Fig. 16. The structure of coumarin-3-carboxylic acid (**35**).



Mendiaxon (**36**) coumachlor (**37**)

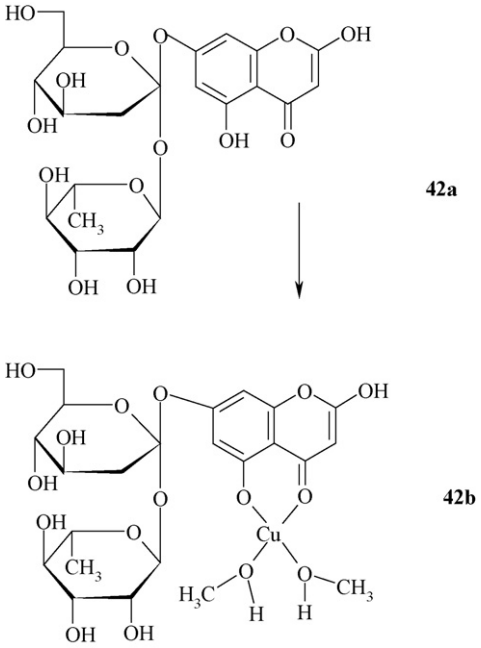
niffcumar (**38**)

Fig. 17. The structure of mendiaxon (**36**), coumachlor (**37**) and niffcumar (**38**).

Lanthanide compounds of mendiaxon (7-hydroxy-4-methyl-coumarin) (**36**, Fig. 17), warfarin (**31**, Fig. 17), coumachlor (4-hydroxy-3-[1-(4-chloro-phenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one) (**37**, Fig. 17), and niffcoumar (4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one) (**38**, Fig. 17) display antitumor activity against P3HR1, K-562, and THP-1 cell lines. These metallorganic complexes indicated stronger cell proliferation-inhibiting effects than the inorganic salts [68].

Similar to the aforementioned lanthanides, platinum Pt(II) (**41**, Fig. 18) and palladium Pd(II) complexes (**40**, Fig. 18) with 3-ethanimidoyl-2-methoxy-2*H*-1,2-benzoxaphospinin-4-ol-2-oxide (1) (**39**, Fig. 18) indicate potent cytotoxic activity against K562, and, additionally, towards HL-60 and NALM-6 leukemia cell lines. They have cytotoxicity coefficients IC_{50} as high as those of cisplatin and carboplatin. Moreover, they may induce an apoptosis pathway shortly after the exposure [69].

Also lanthanide complexes of **36**, **31**, **37** and **38** demonstrate activity against P3HR1, K-562 and THP-1 cell lines. The complexes of cerium, lanthanum and neodymium, with these coumarin ligands, cause approximately 30% inhibition of the survival P3HR1 Burkitt lymphoma cells at concentrations 100 μM. Similarly, the cerium and lanthanum complexes of mendiaxon and niffcoumar have weak cytotoxic effects on AML derived THP-1 myeloleukemia cells [14].



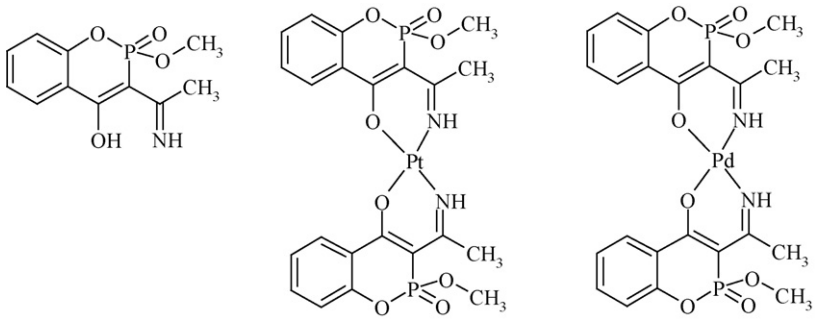
42a

42b

Fig. 19. The structure of naringin (**42a**); proposed structure of complex naringin with copper (**42b**) [74].

Zirconium complexes with compound **39**, show highest cytotoxic activity against human promyelocytic leukemic HL-60 cells than zirconium with warfarin (**31**), coumachlor (**37**) or niffcoumar (**38**) [14,70]. The complexes of cerium(III) and neodymium(III) with **36** demonstrated very low cytotoxic activity against transformed leukemic cell lines (P3HR1 and THP-1) compared to the inorganic salts [55]. In addition, the lanthanum and neodymium complexes with niffcoumar effectively inhibit cells proliferation by about 70%, hence demonstrating more cytotoxic effects than the cerium complex. These results are therefore very promising for cancer treatment [14].

Free naringin (**42a**, Fig. 19) binds Cu(II) ion through the interaction of the Cu(II) ion with the condensed ring (**42b**, Fig. 19) via the carbonyl group in position 4 and by the oxygen of the hydroxyl group in position 5 [30]. Naringin, which possesses antioxidant and cell-cycle stimulating properties, initiates the first stage of the K562, B16F10 and 3T3 cells proliferating process within 24 h, but



39 40 41

Fig. 18. The structure of the 3-ethanimidoyl-2-methoxy-2*H*-1,2-benzoxaphospinin-4-ol-2-oxide (**39**) and its Pd(II) (**40**) and Pt(II) *cis*-complexes (**41**).

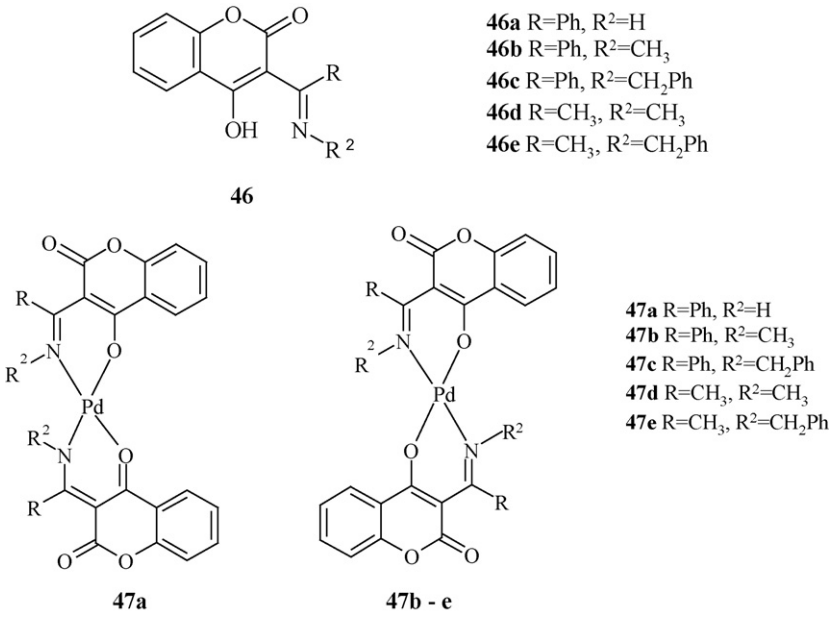


Fig. 20. The structure of coumarin derivatives (**46a**–**e**) and Pd(II)–coumarin-derivative complexes (**47a**–**e**).

causes a decrease in cell number after 48 h of treatment. However, the complex of **42** disturbs growth in all types of cell and causes their death after 24 h of treatment at two different concentrations (50 and 100 μM). In addition, the complex is three times more effective at killing cells than free naringin (**42a**). Also a compound **42b** demonstrates higher anti-inflammatory and antioxidant activity than free naringin. The increase in biological activity of **42b** complex could be associated with the coordination of Cu(II) in positions 4 and 5 of the condensed naringin ring [71].

Also pyrazoloacridine (PA) (**43a**) which can intercalate with DNA, showed antitumor activity in Phase I trials and currently undergoes Phase II testing in several solid tumors. It is well known that PA-cisplatin complex (**43b**) has a synergistic cytotoxic effect in various cell lines such as A549 HCT8, and T98G cells but not MCF-7 and K562 cells. It also renders the removal of platinum-DNA adducts more difficult. Moreover, even at concentrations as low as 0.25 pM, PA is able to partially inhibit the DNA repair process. Various *in vitro* studies have shown that compound **43a** inhibits topoisomerase II and topoisomerase I, which bind to platinated DNA and are involved in its repair [72].

Other studies have suggested different modes of action for the **43b** depending on the cell type. Cells which express wild-type P53 [73] such as A549 cells, or mutant P53 such as T98G cells, show greater than additive cytotoxicity after exposure to the **43b**. However, MCF-7 cells, which express wild-type P53, and K562, without P53, indicate less than additive effects. The mechanism of this phenomenon is, as yet, unknown. As the Pt(II)–AP complex possesses various toxicities, such as myelosuppression for **43a** and nephrotoxicity for cisplatin, and appear to have activity in ovarian cancer, undoubtedly it soon will be studied clinically [74].

The K562 cell cultures undergo apoptosis after treatment by anticancer drugs. In these types of cells, the 5 μM solutions of complexes of 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid methyl ester (**44**) and 5-(2-hydroxyphenyl)-3-methyl-1-(pyridylo)-1*H*-pyrazole-4-carboxylic acid methyl ester (**45**) with platinum(II), palladium(II) and copper(II) exert anti-proliferating activity. A similar effect has been observed in L1210 cells with IC_{50} of 1 μM. Compound **45** alone has less influence on cellular proliferation than its complexes with Pt(II), Pd(II), and Cu(II). In the K562 cell line while 200 μM concentration of Pt(II) and Cu(II) complexes causes death of almost all cells, complexes with Pd(II) at the same concentration were able to kill only 10% of cells – a similar result to the ligand alone. Cisplatin (**20**) at a concentration 51 μM possesses the highest cytostatic ability of all the complexes studied. Numerous experiments on K562 cells have shown that complexes of Cu(II) or Pt(II) cause, approximately, a 2–3-fold increase in cells differentiation. Pd(II) complexes or compound **45** do not affect the tumor cells differentiation [4].

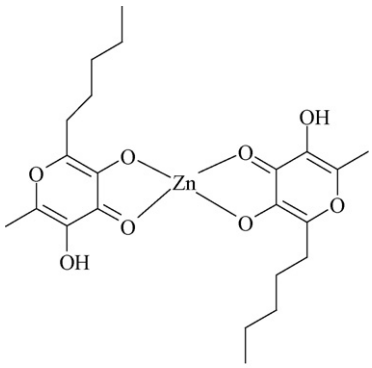
We indicated that palladium(II) complexes with unsubstituted coumarin or *N*-alkylated (methyl or benzyl group) derivatives (**47a**–**e**, Fig. 20) are cytotoxic against NALM-6 and HL-60, but the effect on NALM-6 is higher. Those complexes were obtained in reactions of 2-phenyl-4-oxo-4*H*-chromone-3-carboxylic acid ethyl ester and 2-methyl-4-oxo-4*H*-chromone-3-carboxylic acid methyl ester with amines. *cis*-Palladium complex (**47a**) is more cytotoxic towards leukemia cells (IC_{50} at 4.5 μM for HL-60 and 2.4 μM for NALM-6) than other complexes (**47b**–**e**, Fig. 20) investigated and its activity is similar to that of carboplatin. The cytotoxic activity of palladium complexes with coumarins depends on the structure of the substituents at the nitrogen atom. Moreover, the high cytotoxicity correlates with low stability of complexes **47**. Complex **47**, obtained in reaction of 2-methyl-4-oxo-4*H*-chromone-3-carboxylate (**46**) with aqueous ammonia, possesses high cytotoxic activity also against K562 cells. It exists in two tautomeric forms (**47**, Fig. 20) with proton magnetic resonances for NH and OH groups at δ 9.99 and 12.32 ppm, respectively. Complex **47**, which is an analog of carboplatin (**4**), indicates high cytotoxic activity against the cell line mentioned above (IC_{50} value reached 0.0078 μM, while for carboplatin IC_{50} value reached 60.92 μM) and the ligand did not indicate any toxicity for this cell line. Complex (**25**) is able to moderates aromatic amine (NBP) which mimics the nucleobases in DNA [5].

4.3.2. Human lung cancer and cervical cancer

Palladium–coumarin-derived complex **47** indicates also high cytotoxic activity against A549 and HeLa cells (with IC_{50} value of 0.0097 and 0.0078 μM, respectively), while for carboplatin IC_{50} values reached 105.98, 73.49), the ligand did not indicate any toxicity for all cell lines [5].

4.3.3. Melanoma and lung cancer

The *cis*-Pt(II) complex of 3-aminoflavone (**34b**) invokes apoptosis and decreases the expression of *P53* and *BAX* (BAX belongs



49

Fig. 21. The structure of bis(allixianto) zinc{Zn(alx)$_2$} (**49**).

to a pro-apoptotic group BCL-2, which, in some cell types, is a transcriptional target for *P53*). The complex of **34b** cannot influence the level of *P53* mRNA expression, while *cis*-DDP (*cis*-diaminedichloroplatinum(II)) causes as much as a 25-fold increase of expression after 12 h incubation. After treatment with the *cis*-Pt(II) complex of **34b** the *BAX* expression is lower than in normal lymphocytes treated with the **34b**, which may suggest that it has a less destructive influence on DNA than *cis*-DDP. The **34b** complex is able to inhibit leukemia development in mice after L1210 cell implantation [75–77].

4.4. Diabetes mellitus

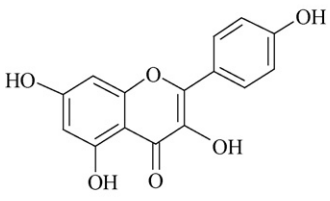
Diabetes mellitus (DM) – impaired carbohydrate, fat, and protein metabolism due to lack of insulin secretion or decreased insulin activity in resistant tissues [69,78]. Zinc complexes with allixin (3-hydroxy-5-methoxy-6-methyl-2-pentyl-4*H*-pyran-4-one): (allixinato)zinc (**48**) and bis(allixinato)zinc [Zn(alx)$_2$] (**49**, Fig. 21) are effective anti-diabetic drugs against type 2 in DM KKA^y mice (a rodent model of non-insulin-dependent diabetes mellitus). They can also, in pretreatment with insulin, inhibit free fatty acid (FFA) release from the cells after treatment with epinephrine in a dose-dependent manner. Moreover 50 μM $ZnCl_2$ is not able to induce this process [79,80]. Some flavonoids such as kaempferol (**12a**), kaempferitrin (**50a**) and kaempferol-3-neohesperidoside (**12b**) possess anti-diabetes and insulin-mimetic activity because of their anti-hyperglycemic effect. Properties of this compounds are increased by complexation with VO(IV). Compound of each ligand possesses the keto-phenol group which is coordinated to the metal ion [81].

In the case of the kaempferitrin complex with VO(IV), the VOH_2L_2 (VO(IV) bound with monodeprotonated kaempferitrin at 1:2 ratio) (**50b**, Fig. 22) is a major species at physiological pH. It possesses two bulky ligands contributing to the steric hindrance of the complex. Its effect on cells is similar to that of **50a** alone, probably because the VO(IV) ion is beset by two molecules of kaempferitrin compound **50a**, disallowing vanadium ion to bind to the receptor (and/or glucose carriers). Hypoglycemic activity of this compound is probably caused by OH groups at the B rings of the **50a** molecules [81].

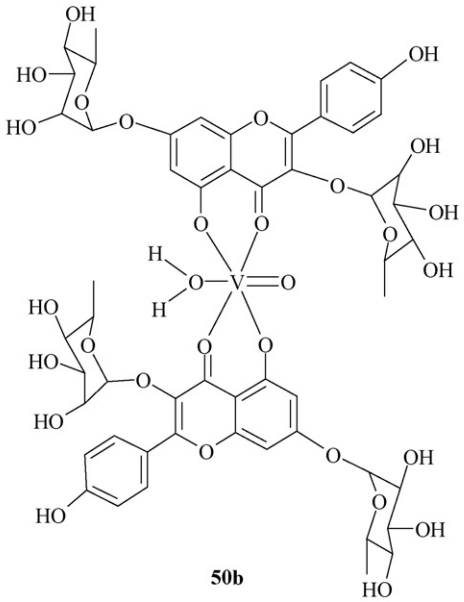
Bis(quercetinato)oxovanadium(IV) (**51**) also possesses hypoglycemic and mitogenic activity in both type 1 and type 2 diabetes. It is able to change the level of glucose and influence the synthesis of glycogen in the diaphragm, liver and fat cells. It also improves glucose transport and oxidation in adipocytes and skeletal muscles *in vitro* in rat tissue. The examination of vanadium complexes as potential anti-diabetes drug seems to be based on the potential insulin mimetic activity of those complexes [82,83].

4.5. Huntington's disease

Huntington's disease is a neurodegenerative disorder connected with lesions in the striatum of the brain that cause progressive behavioral and cognitive impairments and involuntary choreiform movements [84]. Copper(II) and iron(II) ions levels are increased in the striatum of HD patients. One factor that is believed to be involved in HD is a protein called hungtingtin. The increased level of copper(II) is involved in huntingtin aggregation and redox-activity. Epigallocatechin-gallate (**19**), a flavonoid extracted from green tea is a copper chelator which is able to modulate early disorders in huntingtin folding [85,86].

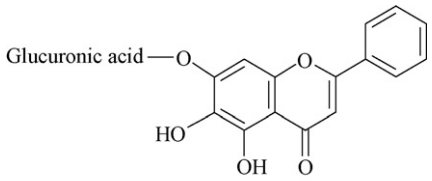


50a



50b

Fig. 22. Possible structure of kaempferitrin (**50a**) and the kaempferitrin–VO(IV) complex (at physiological pH) (**50b**).



53

Fig. 23. The structure of baicalin (**53**).

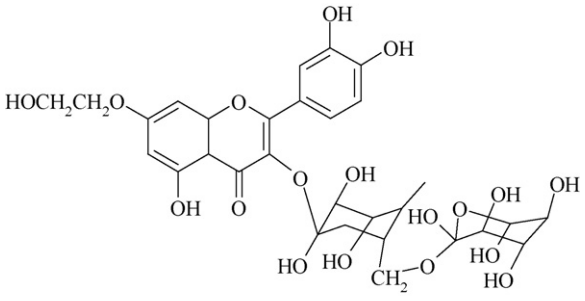
4.6. β-Thalassemia

β-Thalassemia is a hereditary disease caused by excessive extravascular hemolysis because of abnormal hemoglobin synthesis. Patients, who have β-thalassemia major, which is one of β-thalassemia types which causes severe hemolysis, require multiple blood transfusion. Moreover in the absence of iron chelating treatment, iron overload occurs. Excess of body iron ions causes that increased free iron ions induces free radical oxygen species (ROS) as in Fenton's reaction [87]:

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\bullet}OH + OH^{-}$$

Patients with β-thalassemia accumulate high levels of iron in their tissues, in two ways: directly, or by repeated blood transfusions. Typical symptoms of β-thalassemia major are anemia, iron overload, increased production of reactive oxygen species (ROS), which can cause damage to major organs, especially the cardiovascular system [88]. This process rapidly leads to death through cardiac failure, so it's vital to find an effective remedy to control the iron level. A common consequence of β-thalassemia is excessive iron deposition in the liver which can cause further complications such as fibrosis [89]. The usage of chelators can ameliorate the symptoms of iron overload and improve the quality of life and overall survival rate for sufferers. A standard cure for β-thalassemia is deferoxamine and 1,2-dimethyl-3-hydroxypyrid-4-one (deferiprone, L1) (**52**), however although they are very effective, they cause various side effects [89,90]. A search for new, effective drugs that lack serious side effects has not brought spectacular results yet, however, it is widely agreed that an effective drug (chelator) should possesses antioxidant properties [90,91]. Researchers have indicated that some flavonoids possess direct influence on iron(III) ions level within tissues. For example, baicalin (**53**, Fig. 23) is able to combine with hepatic non-heme iron and mobilize them into the blood stream and remove them from the organism. Moreover it inhibits the iron-catalyzed oxidative reactions. Compound **53** also decreases lipid peroxidation in iron overload mice liver [91,92].

7-Monohydroxyethylrutoside (monoHER) (**54**, Fig. 24), a semi-synthetic flavonoid which possesses antioxidant properties, is able to bind iron ions [93,94]. MonoHER treatment decreased plasma iron ions level in β-thalassemic mice. It also increased vitamin E level in erythrocytes lipid membranes, and decreased binding of IgG to erythrocytes lipid membrane. Survival of erythrocytes as T_{50} (survival of 50% of population) was not prolonged, however T_{20} (survival of 20% of population) time was prolonged. These facts suggest that compound **54** can act as preventive agent against free radicals [95].



54

Fig. 24. The structure of monoHER (**54**).

5. Flavonoids–metal complexes as a remedy for various diseases

5.1. Bacterial infections

Kopacz et al. indicated that complexes of morin (**55**) with La(III), Gd(III) and Lu(III) ions inhibit bacterial strains like *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. La(II)–morin complex was the most effective inhibitor against *E. coli* at all tested concentration (from 0.15 to 6.0 μg/ml). Only the Gd(III)–morin complex showed activity against *K. pneumoniae* at concentration higher than 0.3 μg/ml. Both La(III)– and Gd(III)–morin complexes were effective against *S. aureus* at the same minimal inhibitory concentration (MIC) – 0.75 μg/mL. While Lu(III)–morin complex did not inhibit significantly the grow of the tested strains [96]. Also, complexes of Pd(II) and bis(benzonitrile)dichloropalladium(II) $[PdCl_2(PhCN)_2]$ with (*E*)-3{[(diethoxythiophosphoryl)-methylhydrazone]-methylene}-4-hydroxy-2*H*-1-benzopyran-2-one (**56**), (*E*)-3-{[(dimethoxythiophosphoryl)-methylhydrazine]-methylidene}-3,4-dihydro-2*H*-1-benzo-pyran-2,4-dione (**57**), (*E*)-3-{[(diethoxythiophosphoryl)-hydrazone]-methylene}-4*H*-1-benzopyran-4-one (**58**) possess low antibacterial activity against *S. aureus* ATCC 6538P and *Pseudomonas aeruginosa* ATCC 27853. Compounds **56** and **57** are created by reacting diethyl- or dimethylthiophosphorohydrazide with methylchromone-3-carboxylate. Spectroscopic studies have shown that these compounds **56** and **57** possess two tautomeric forms in solution and 4-hydroxycoumarin derivatives predominate. Phosphorohydrazone of chromone **58** was obtained by the reaction of 3-formylchromone with diethoxythiophosphorylhydrazide. The complexes of $[PdCl_2(PhCN)_2]$ with ligands **56**–**58** were prepared in the reaction with thiophosphorohydrazones [97,98].

6. Summary

In this paper we have presented the biological activities of some complexes of coumarins, chromones and flavonoids with some metals ions like copper(II) or iron(III). Numerous studies of the complexes mentioned above indicated that they could be the future of effective treatment due to its wide field of action. Although mentioned in this paper complexes of warfarin with La(III) ions, which have been used in HIV treatment, possess quite a low activity, they showed the way for further research for a HIV remedy.

The complexes mentioned above also may be support alleviation of the effects of incurable diseases like Wilson disease or β-thalassemia. In β-thalassemia treatment they could be an alternative for toxic deferoxamine and deferiprone, while the aniline derivatives which include coumarin moiety with metal complexes can be used as detectors of Menkes disease or Wilson's disease. Moreover if Zn-allixin and bis(allixinato)zinc $[Zn(alx)_2]$ are effective drugs against type 2 diabetes in mice, probably they also could be effective against human diabetes. Some complexes like the palladium–coumarin-derived complex (**47**) which is cytotoxic against HeLa cells, or zirconium-mediaxon complex, which possess cytotoxic activity against HL-60 cells seem to be promising remedies in cancer treatment.

Acknowledgement

This work was supported by grant from the Medical University of Lodz no. 503-3066-2.

References

[1] E. Budzisz, U. Krajewska, M. Różalski, Pol. J. Pharmacol. 56 (2004) 473.
[2] M.C. Foti, S.K. Sharma, G. Shakya, A.K. Prasad, G. Nicolosi, P. Bovicelli, B. Ghosh, H.G. Raj, R.C. Rastogi, V.S. Parmar, Indo-Italian CSIR-CNR Project 2005.
[3] E. Budzisz, M. Małecka, I.-P. Lorenz, P. Mayer, R.A. Kwiecień, P. Paneth, U. Krajewska, M. Różalski, Inorg. Chem. 45 (2006) 9688.
[4] M. Miernicka, A. Szulawska, M. Czyz, I.-P. Lorenz, P. Mayer, B. Karwowski, E. Budzisz, J. Inorg. Biochem. 102 (2008) 157.
[5] E. Budzisz, B.K. Keppler, G. Giester, M. Woznicka, A. Kufelnicki, B. Nawrot, Eur. J. Inorg. Chem. 22 (2004) 4412.
[6] E. Budzisz, B.K. Keppler, M. Małecka, B. Keppler, V.B. Arion, G. Andrijewski, U. Krajewska, M. Różalski, Eur. J. Inorg. Chem. 23 (2007) 3728.
[7] R. Sancho, N. Márquez, M. Gómez-Gonzalo, M.A. Calzado, G. Bettoni, M.T. Coiras|, J. Alcamí, M. López-Cabrera, G. Appendino, E. Muñoz, J. Biol. Chem. 279 (2004) 37349.
[8] A.M.S. Silva, D.C.G.A. Pinto, J.A.S. Cavaleiro, A. Levai, T. Patonay, ARKIVOC Part 7 106 (2004) 123, ISI:000224153300009.
[9] D.O. Bennardi, G.P. Romanelli, J.L. Jios, J.C. Autino, G.T. Baronetti, H.J. Thomas, ARKIVOC (2008) (xi) 123.
[10] M. Recanatini, A. Bisi, A. Cavalli, F. Belluti, S. Gobbi, A. Rampa, P. Valenti, M. Palzer, A. Palusczak, R.W. Hartmann, J. Med. Chem. 44 (2001) 672.
[11] W.H. Gerwick, J. Nat. Prod. 52 (1989) 252.
[12] N. Gambhir, G. Krishnamurty, H.G. Indian, J. Chem. 40B (2001) 278.
[13] L.D. Raev, E. Voinova, I.C. Ivanov, D. Popov, Pharmazie 45 (1990) 696.
[14] I. Kostova, Curr. Med. Chem. - Anti-Cancer Agents 5 (2005) 29.
[15] R.S. Hoult, M. Payá, Gen. Pharmacol. 27 (1996) 713.
[16] I. Kostova, G. Momekov, P. Stancheva, Hindawi Publishing Corporation Metal-Based Drugs (2007) Article ID 15925, doi:10.1155/2007/15925.
[17] E.J. Lien, S. Ren, H.H. Bui, R. Wang, Free Radic. Biol. Med. 14 (1999) 285.
[18] E. Budzisz, E. Brzezinska, U. Krajewska, M. Różalski, Eur. J. Med. Chem. 38 (2003) 597.
[19] M.L. Neuhouser, Nutr. Cancer 50 (2004) 1.
[20] J.B. Harborne, C.A. Williams, Phytochemistry 55 (2000) 481.
[21] J.A. Ross, C.M. Kasum, Annu. Rev. Nutr. 22 (2002) 19.
[22] X. Wang, M.E. Morris, Drug Metab. Dispos. 35 (2007) 268.
[23] J. Lu, L.V. Papp, J. Fang, S. Rodriguez-Nieto, B. Zhivotovsky, A. Holmgren, Cancer Res. 66 (2006) 4410.
[24] W. Samee, P. Nunthanavanit, J. Mol. Sci. 9 (2008) 235.
[25] L. Reznichenko, T. Amit, H. Zheng, Y. Avramovich-Tirosh, M.B.H. Youdim, O. Weinreb, S. Mandel, J. Neurochem. 97 (2006) 527.
[26] Q. Guo, B. Zhao, M. Li, S. Shen, W. Xin, Biochim. Biophys. Acta 1304 (1996) 210.
[27] N. Grinberg, H. Newmark, N. Kitrossky, E. Rahamim, M. Chevion, E.A. Rachmilewitz, Biochem. Pharmacol. 54 (1997) 973.
[28] Y. Levites, T. Amit, S. Mandel, M.B.H. Youdim, FASEB J. 17 (2003) 952.
[29] S.C. Burdette, S.J. Lippard, Meeting of the minds: metalloneurochemistry, PNAS 100 (2003) 3605.
[30] D.W. Domaille, E.L. Que, C.J. Chang, Nat. Chem. Biol. 4 (2008) 168.
[31] M.P. Mattson, Nature 430 (2004) 631.
[32] H.-F. Ji, H.-Y. Zhang, J. Mol. Struct.: THEOCHEM 767 (2006) 3.
[33] G. Multhaup, A. Schliksupp, L. Hesse, D. Beher, T. Ruppert, C.L. Masters, K. Beyreuther, Science 271 (1996) 1406.
[34] P.C. Pauly, D.A. Harris, J. Biol. Chem. 273 (1998) 33107.
[35] L. Rossi, E. Marchese, M.F. Lombardo, G. Rotilio, M.R. Ciriolo, Free Radic. Biol. Med. 30 (2001) 1177.
[36] N. Bilenko, M. Yehie, Y. Inbar, E. Gazala, Israel Med. Assoc. J. 9 (2007) 521.
[37] G.P. Andreu, R. Delgado, J.A. Velhoa, C. Curtid, A.E. Vercesi, Eur. J. Pharmacol. 513 (2005) 47.
[38] E.R. Jamieson, S.J. Lippard, Chem. Rev. 99 (1999) 2467.
[39] J.T. Hartmann, H.P. Lipp, Expert Opinion Pharmacother. 4 (2003) 889.
[40] T. Boulikas, A. Pantos, E. Bellis, P. Christofis, Cancer Ther. 5 (2007) 537.
[41] M. Pavelka, M.F. Lucas, N. Russo, Chemistry 13 (2007) 10108.
[42] R.F.V. de Souza, W.F. De Giovani, Redox Rep. 9 (2004) 97.
[43] H. Tang, X. Wang, S. Yang, L. Wang, Rare Met. 23 (2004) 38.
[44] S. van Acker, G.P. van Balen, B. van der Berg, W.J.F. Van der Vijgh, Biochem. Pharmacol. 56 (1998) 935.
[45] I.B. Afanas'ev, A.I. Dorozhko, A.V. Brodskii, V.A. Kostyuk, A.I. Potapovitch, Biochem. Pharmacol. 38 (1989) 1763.
[46] D. Malešev, V. Kunti, J. Serb. Chem. Soc. 72 (2007) 921.
[47] M.E. Bodini, G. Copia, R. Tapia, F. Leighton, L. Herrera, Polyhedron 18 (1999) 2233.
[48] J.P. Cornard, J.C. Merlin, J. Inorg. Biochem. 92 (2002) 19.
[49] J. Zhou, L. Wang, J. Wang, N. Tang, J. Inorg. Biochem. 83 (2001) 41.
[50] N. Yamashita, H. Tanemura, S. Kawanishi, Mutat. Res. 425 (1999) 107.
[51] B.G. Turner, M.F. Summers, J. Mol. Biol. 285 (1999) 1.
[52] P.G. Yeni, S.M. Hammer, C.C. Carpenter, D.A. Cooper, M.A. Fischl, J.M. Gatell, B.G. Gazzard, M.S. Hirsch, D.M. Jacobsen, D.A. Katzenstein, J.S. Montaner, D.D. Richman, M.S. Saag, M. Schechter, R.T. Schooley, M.A. Thompson, S. Vella, P.A. Volberding, J. Am. Med. Assoc. 288 (2002) 222.
[53] D. Yu, M. Suzuki, L. Xie, S.L. Morris-Natschke, K.-H. Lee, Med. Res. Rev. 23 (2003) 322.
[54] P. Zhou, Y. Takaishi, H. Duan, B. Chen, G. Honda, M. Itoh, Y. Takeda, O.K. Kodzhimatov, K.-H. Lee, Phytochemistry 53 (2000) 689.
[55] I. Manolov, I. Kostova, S. Konstantinov, M. Karaivanova, Eur. J. Med. Chem. 34 (1999) 853.
[56] D.C. Montefiori, W.E. Robinson Jr., S.S. Schuffman, W.M. Mitchell, J. Clin. Microbiol. 26 (1988) 231.
[57] Z. Tümer, N. Horn, J. Med. Genet. 34 (1997) 265.
[58] M.L. Schilsky, Semin. Liver Dis. 6 (1996) 83.
[59] M.X. Wang, X.M. Meng, M.Z. Zhu, Q.X. Guo, Chin. Chem. Lett. 18 (2007) 1403.
[60] S. Fakih, M. Podinovska, X. Kong, U.E. Schaible, H.L. Collins, R.C. Hider, J. Pharmaceut. Sci., doi:10.1002/Jps.
[61] R.S. Go, A.A. Adjei, J. Clin. Oncol. 17 (1999) 409.
[62] R.J. Knox, F. Friedlos, D.A. Lydall, Cancer Res. 46 (1986) 1972.
[63] K. Kostka, Rocz. Chem. 47 (1973) 305.
[64] M.E. Heim, in: B.K. Keppler (Ed.), Metal Complexes in Cancer Chemotherapy, VCH, Weinheim, 1993, p. 9.
[65] E. Ciesielska, K. Studzian, E. Zyner, J. Ochocki, L. Szmigiero, Cell. Mol. Biol. Lett. 5 (2000) 441.
[66] B. Kosmider, I. Zawlik, P.P. Liberski, R. Osiecka, E. Zyner, J. Ochocki, J. Bartkowiak, Mutat. Res. 604 (2006) 28.
[67] I. Kostova, I. Manolov, I. Nicolova, S. Konstantinov, M. Karaivanova, Eur. J. Med. Chem. 36 (2001) 339.
[68] B. Arezzini, B. Lunghi, G. Lungarella, C. Gardi, Int. J. Biochem. Cell Biol. 35 (2003) 486.
[69] B.B. Turkoski, Orthop. Nurs. 25 (2006) 227.
[70] I. Kostova, M. Manolov, Karaivanova, Arch. Pharm. (Weinheim) 334 (2001) 157.
[71] R.M.S. Pereira, N.E.D. Andrades, N. Paulino, A.C.H.F. Sawaya, M.N. Eberlin, M.C. Marcucci, G.M. Favero, E.M. Novak, S.P. Bydlowski, Molecules 12 (2007) 1352.
[72] J.P. Eder, V.T.-W. Chan, S.-W. Ng, N.A. Rizvi, S. Zacharoulis, B.A. Teicher, L.E. Schnipper, Cancer Res. 55 (1995) 6109.
[73] K.J. Russell, L.W. Wiens, G.W. Demers, D.A. Galloway, S.E. Plon, M. Groudine, Cancer Res. 55 (1995) 1639.
[74] A.A. Adjei, I. Imawati Budihardjo, E.K. Rowinsky, T.J. Kottke, P.A. Svingen, C.A. Buckwalter, L.B. Grochow, R.C. Donehower, S.H. Kaufmann, Clin. Cancer Res. 3 (1997) 761.
[75] J.H. Choi, K.S. Ahn, J. Kim, Y.S. Hong, Exp. Mol. Med. 32 (2000) 23.
[76] E. Zyner, J. Graczyk, J. Ochocki, Pharmazie 54 (1999) 945.
[77] B. Zurowska, A. Erxleben, Ł. Glinka, M. Łeczycka, E. Zyner, J. Ochocki, Inorg. Chim. Acta (2008) doi:10.1016/j.ica.2008.04.014.
[78] A.C. Guyton, J.E. Hall (Eds.), Textbook of Medical Physiology, 11th ed., Elsevier Saunders, Philadelphia, 2006.
[79] M. Schweiger, R. Schreiber, G. Heammerle, A. Lass, C. Fledelius, P. Jacobsen, H. Tornqvist, R. Zechner, R. Zimmermann, J. Biol. Chem. 281 (2006) 40236.
[80] A. Nakayama, M. Hiromura, Y. Adachi, H. Sakurai, J. Biol. Inorg. Chem. 13 (2008) 675.
[81] L.H. Cazarolli, L. Zanatta, A.P. Jorge, E. de Sousa, H. Horst, V.M. Woehl, M.G. Pizzolatti, B. Szpoganicz, F.R.M. Barreto Silva, Chemico-Biol. Interact. 163 (2006) 177.
[82] A.S. Clark, J.M. Fagan, W.E. Mitch, Biochem. J. 232 (1985) 273.
[83] K.C. Ong, H.E. Khoo, Biochem. Pharmacol. 51 (1996) 423.
[84] R.K. Graham, Y. Deng, E.J. Slow, B. Haigh, N. Bissada, G. Lu, J. Pearson, J. Shehadeh, L. Bertram, Z. Murphy, S.C. Warby, C.N. Doty, S. Roy, C.L. Wellington, B.R. Leavitt, L.A. Raymond, D.W. Nicholson, M.R. Hayden, Cell 125 (2006) 1179.
[85] K.S. Ghosh, T.K. Maiti, A. Mandal, S. Dasgupta, FEBS Lett. 580 (2006) 4703.
[86] J.H. Fox, J.A. Kama, G. Lieberman, R. Chopra, K. Dorsey, et al., PloS ONE 2 (2007) e334, doi:10.1371/journal.pone.0000334.
[87] T. Dissayabutra, P. Tosukhowong, P. Seksan, J. Med. Assoc. Thailand 88 (2005) 317.
[88] M.A. Ebrahimzadeh, F. Pourmorad, A.R. Bekhradnia, Afric. J. Biotechnol. 7 (2008) 3188.
[89] C. Gardi, B. Arezzini, V. Fortino, M. Comporti, Biochem. Pharmacol. 64 (2002) 1139.
[90] D.R. Richardson, Expert Opin. Investig. 8 (1999) 2141.
[91] Y. Zhao, H. Li, Z. Gao, H. Xu, Eur. J. Pharmacol. 509 (2005) 195.
[92] R.P. Hebbel, A. Leung, N. Mohandas, Blood 76 (1990) 1015.
[93] S.A.B.E. Van Acker, D.J. Van den Berg, M.N. Tromp, D.H. Griffioen, W.P. Van Bennekom, W.J.F. Van der Vijgh, A. Bast, Free Radic. Biol. Med. 20 (1996) (1996) 331.
[94] F.A.A. Van Acker, S.A.B.E. Van Acker, K. Kramer, G.R.M.M. Haenen, W.J.F. Van der Vijgh, A. Bast, Clin. Cancer Res. 6 (2000) 1337.
[95] L. De Franceschi, S.F. Turrini, M. Honczarenko, K. Ayi, A. Rivera, M.D. Fleming, T. Law, F. Mannu, F.A. Kuypers, A. Bast, W.J.F. Van der Vijgh, C. Brugnara, Haematologica 89 (2004) 1287.
[96] M. Kopacz, E. Woźnicka, J. Gruszecka, Acta Pol. Pharmaceut. - Drug Res. 62 (2005) 65.
[97] A.J. Rybarczyk-Pirek, S.J. Grabowski, J.J. Nawrot-Modranka, Phys. Chem. A 107 (2003) 9232.
[98] J. Nawrot-Modranka, E. Nawrot, Acta Pol. Pharmaceut. - Drug Res. 63 (2007) 429.