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CHEMISTRY
Mini-Review

Synthesis and Structure of Cobalt Coordinated Molecules with Anticancer Activity: Recent Advances and Some General Considerations

Manolis Vlasiou*

University of Cyprus, Department of Chemistry, Cyprus, Nicosia

***Corresponding Author:** Manolis Vlasiou, University of Cyprus, Department of Chemistry, Cyprus, Nicosia.

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Abstract

This mini-review is focused to the latest advances of the last five years regarding the synthetic strategies and the evaluation of the biological activity of coordinated cobalt (II)/(III) compounds. The structures are much closed connected with the activity of the molecules related with chelation to metal center which is also a piece of discussion in this work. The review is also engaged to discuss the future possibilities of the anticancer activity of cobalt complexes.

Keywords: *Cobalt, complexes, anticancer, activity, synthesis, structure.*

Abbreviations: A-549: human lung adenocarcinoma cell line; MDA-361: human epithelial breast cancer; SW620: human colon carcinoma cell line; Hela: human cervix cancer cell line; HepG2: human hepatoma carcinoma cell line; MDA-MB-435: human breast carcinoma cell line; PC-3: prostate cancer cell-line.

Introduction

Transition metal complexes with their tunable coordination geometry, redox activity and spectroscopic properties are suitable for designing metal-based therapeutic agents to control primary and malignant secondary tumors. After the successful use of Cisplatin against several types of cancer, a vast number of inorganic compounds have been introduced in the research field of metal-based drugs. It has been well understood that the use of transition metals increased the biological activity of anticancer drugs. This well-known action is mimicking the active site of several enzyme molecules and co-enzymes, which was also made from metal ions [1].

In some cases, the bioactivities of these compounds have been shown to depend on both hexacarbonyldicobalt moiety and the organic ligand. The modes of action are as varied as their structures. Some affect cell proliferation by modulating cellular oxidative stress, either by releasing carbon monoxide or by generative reactive oxygen species.

The transfer proteins in human serum blood are very important for human health because of their responsibility to bind in specified drugs and transferred them to the area of action. For that reason is in great interest the vehicle that drives the metal ion, the biological activity of the ligand - vehicle, the type of bonding with protein and the level of the molecule stability. These factors are controlled by the structure of the molecule. The coordinated compounds have much more rearrangements in the 3D space than the pure organic ones and different oxidation states that are responsible for radical scavenging (to reduce the possibility of tumor growth) or radical induce (to program a cancer cell apoptosis). For both cases, the strategic synthesis of a ligand is in the great interest and it must not be underestimated. Some analogues due the structure are targeting cellular DNA; other organometallics owe their activity to the inhibition of kinases, proteases, esterase's, or other enzymes. Moreover, it has to be clear that the physicochemical characteristics of the metal ions are in a great consideration as well.

Cobalt is an element of biological interest because its biological role is mainly focused on its presence on the active center of vitamin B12, regulating indirectly the DNA synthesis. A reason for the evaluation of cobalt ion in this work is the relatively small number of studies that are connected with cobalt-based drugs. In addition, the synthesis of a pro-drug has to based upon the action taking place inside the cell membrane or over the cell of different sites of the cells. A great knowledge about the level of hydrophilicity or hydrophobicity of the molecule has to be considered as well. These reasons leading to a necessity of a systematic review over the advances has been made upon this time in this research field. More specifically the lack of a review over the recent advances upon anticancer cobalt based molecules and the connection between synthesis, structure and activity was a reason for this work.

Herein, are described the synthetic strategies and geometrical conformation of cobalt coordinated molecules and their anticancer activity studied, over the last five years.

Synthesis and structure of biological active cobalt complexes

There are several synthetic procedures for the preparation of Co (II) and Co (III) coordination compounds, especially for cobalt complexes with anticancer activity. The most common ligands that are in use for anticancer activity are tridentate N,O- donor ligands, phenathroline based ligands, isoflavones ligands and ketoaminato ligands. There is a focus in using the +2 and +3 oxidation states of these molecules because this makes the compounds active to the physiological features of tumors. This strategy helps a selective action to the targeted molecules and suppresses the side effects in healthy molecules.

More specifically, in a recent study [2] were synthesized three ligands with electron withdrawing groups.
L1:[(2-hydroxy-5-nitrobenzyl)
L2:(2-(pyridil-2-yl)ethyl]amine) [(2-hydroxybenzyl) (2-(pyridil-2-yl)ethy]imine]
L3: [(2-hydroxy-5-nitrobenzyl) (2-(pyridil-2-yl) ethyl] imine).

The substitutions of groups in the para position of the phenol L1 and the imine instead of the amine L2 and L3, promote anodic shifts in the complexes reduction potentials. These mononuclear complexes obtained with slow addition of $Co(ClO_4)2.6H_2O$ in a methanol solution of L1, L2 and L3giving

C1:$[Co(L1)_2]ClO_4 \bullet 1/3C_2H_5OH$
C2:$[Co(L2)_2]ClO_4 \bullet 1/2CH_3OH$
C3:$[Co(L3)_2]ClO_4 \bullet 5H_2O$.

The crystallographic data indicate mononuclear cation complexes; with Co (III) metal center coordinated to two tridentate N2O-donor ligands, in distorted octahedral geometries. In figure 1 are depicted the L1, L2 and L3 ligand molecules.

Another biological active molecule of Co (III) is the C4:cis-$[Co(phen)_2(C_{14}H_{29}NH_2)]C_{l2} \bullet 3H_2O$ complex molecule with the ligands (L4:phen = 1,10-phenanthroline, L5:$C_{14}H_{29}NH_2$ = tetradecylamine) [3].In this surfactant, the entity is containing the central metal ion Co (III), along with its primary coordination sphere, acts as the head group and hydrophobic entity of the ligand L5 act as the tail part leading the molecule to hydrophobic environments (figure 2). The reaction of pyrogallic acid and p-hydroxyphenylacetic acid among with the addition of N,N-dimethylformamide (DMF) and small portions of methylsulfonyl chloride ($MeSO_2Cl$), gave the ligand L6: 7,8,4'-trihydroxy-isoflavone [4]. The molecule C5: $Co(L5\text{-}H)_2$ was obtain via titration of the acetate metal (II) salt to an ethanol solution of L6in pH 7-8 as shown in figure 3. A series of square planar cobalt (II) compounds with tetradentateβ-ketoaminato complexes is another example of biological active cobalt complexes [5]. The fluorinated β-ketoamine ligands were synthesized by a multi - step reaction with a silylenol protecting group. In addition a tetrahedral cobalt complex with two bidentate β-ketoamine ligands was also synthesized. The complexes formed with the addition of $Co(N(SiMe3)_2)_2$.

L7:bis(hexafluoroacetylacetone)ethylenediimine
L8:(benzoyltrifluoroacetone)ethylenediimine
L9:(benzoylacetonato)phenyleneimineamine
C6:(bis(hexafluoroacetylacetonato)ethylenediimino)cobalt(II)
C7:(bis(benzoyltrifluoroacetonato)ethylenediimino)cobalt(II)
C8:[(benzoylacetonato)phenyleneimineamino)cobalt(II).
L8 is prepared via Schiff base condensation of 1-phenyl-1,3-butanedione and 1,2-diaminoethane in refluxing toluene. L7and L8 prepared by deprotonation of diketone using NaH to produce $[R_1COCHCOR_2]$-Na+salt. The salt treated with tert-butyldimethylchlorosilane to produce a silylenolether which is treated with 1,2-diaminoethane to form the fluorinated β-ketoamine. C7 exhibits a square planar geometry and C8 exhibits a tetrahedral geometry with Co bond lengths to be shorter in square planar C7 than in tetrahedral C8 (figure 3). Another series of $[Co(diimine)_3](ClO_4)_2$ with octahedral coordination geometry complexes (C9, C10 and C11) where diimine=1,10-phenathroline (phen) L10, 5,6-dimethyl-1,10-phenathroline (5,6-dmp) L11 and dipyrido [3,2-d: 2',3'-f]quinoxaline (dpq) L12 evaluated for their anticancer activity [6]. The x-ray crystal structure of C10 consists of both Δ- and Λ-enantiomers of the complex cation and the molecular structure of the complex cation with crystal sphere shape is depicted in figure 4. Moreover, a series of tetrapyridine bases $[Co(L)_2](ClO_4)_2$ were introduced with ligands L13: 4'-phenyl-2,2':6',2''-tetrapyridine (ph-tpy) L14:4'-(9-anthracenyl)-2,2':6',2''-tetrapyridine (an-tpy) L15:4'-(1-pyrenyl)-2,2':6',2''-tetrapyridine (py-tpy). The ligands L13, L14, L15 and the complexes C12, C13 and C14 are depicted in figure 5. These cobalt (II) complexes are prepared from the reaction of $[Co(H_2O)_6](ClO_4)_2$ with tetrapyridine base in methanol and isolated as perchlorate salts. These complexes are having a planar aromatic photo-active moieties displaying visible light and induced plasmid DNA activity [7]. Additionally, a novel dinuclear cobalt (III) complex C15: $[Co_2L_2](NO_3)_2 \bullet 2H_2O \bullet 0.5C_2H_5OH$ with the condensation product of 2-acetylpyridine and malonic acid dihydrazide, L16:N',N'2-bis[(1E)-1-(-pyridyl)ethylidene]propanedihydrazide (ligand) was synthesized and the anticancer activity was observed. The complex was formed with two molecules of L16 coordinated to each cobalt atom and two nitrate ions in the outer sphere were obtained [8]. The complex cation $[Co_2L_2]_{2+}$ possesses a dinuclear double-stranded helicate structure in which each Co (III) center is coordinated by two tridentate N_2O chelating units from different ligands. Each Co (III) center occupies a six - coordinated pseudo octahedral environment surrounded by two chelating units coordinated to Co (III) atom in mer configuration with pairs of carbonyl O atoms and pyridine N atoms in a cis relationship, whereas the hydrazide N atoms are trans to each other. The biological active ligand clotrimazole L17 was used to synthesised C16: $[Co(clotri)2Cl_2]$ C17:$[Co(clotri)_2Br_2]$ and C18:$[Co(clotri)_3(NO_3)_2]$. The tetrahedral Co (II) complexes when crystallized in Et OH displays five coordination square-based pyramid geometry due to the coordination of an ethanol molecule to the metal center [9]. Interesting novel works of cobalt complexes also presented with a water soluble ligand of L18: 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (isonicotinic) hydrazole [9], and a series of L19: scorpionate ligands [11] synthesizing the first tris(pyrazolyl)methane Co (II) complex C19. In figure 6 it is shown the synthetic route of C20:$\{[Co(H_2L)(H_2O)2](NO_3)_2 \bullet 3H_2O\}n$ with ligand L18 bearing octahedral Co (II) species.

In more recent studies, new cobalt compounds C21 and C22 of L20:1, 10-phenanthroline-5,6-dione or L21:1,3,5-tri-aza-7-phosphaadamantane derivatives, were tested against cancer cell lines [12]. C21: [L19][$CoCl_4$], C22:$[CoCl(H_2O)(L20)_2][BF_4]$. The coordination environment of C21 around the Co (III) atom seems to be almost perfect tetrahedron filled by four chloride ions (figure 7).

In the last year, another five different works with great interest reported the synthesis of cobalt complexes with anticancer activity. More specifically, two novel vicinal dioxime ligands containing thiomicarbazone units L22:(2E)-2-[4-(diethylamino)benzyl-idene]-N-[(1Z,2E)-N-hydroxyimino) ethanimidoyl] hydrazine carbothioamide and L23: (2E)-2-[4- (dimethylamino) benzyl-idene] -N-[(1Z,2E) -N-hydroxyimino)ethanimidoyl] hydrazine carbothioamide were synthesised among mononuclear Co (II) complexes, C23 and C24 [13]. The second research work was evaluated the synthesis of complexes C25:$[Co(LH)_2(NCS)]NO_3$ and C26:$[Co(LH)_2(NH_3)]NO_3$ with the use of the potential tetra dentatemonoanionic N_2O_2 chelate ligand L24:2-[{[2-(Dimethylamino)ethyl]imino}methyl]-6-methoxyphenol [14]. The single x-ray diffraction analysis confirms the distorted octahedral geometry around Co (II). In a third work two cobalt(II) complexes C27:$[Co(QCT)_2] \bullet Cl \bullet 1.5H_2O$ L25:(QCT = quinoline-2-carboxaldehydethiosemicarbazone) and C28:$[Co(QCMT)(CH_3OH)Cl_2]$ L26: (QCMT =

quinoline-2-carboxaldehydeN4-methyl-thiosemicarbazone) have been synthesized and structurally characterized [15]. In both complexes, the cobalt(II) center is six - coordinated with distorted octahedral geometry. Finally in the last year novel penta-azamacrocyclic 15-membered [N5] ligand L27: i.e. 1,5,8,12-tetetraaza-3,4: 9,10-dibenzo-6-ethyl-7-methyl-1,12-(2,6-pyrido)cyclopentadecan-5,7 diene-2,11-dione and its transition metal complex with Co(II) C29 showing tetrahedral conformation [16] and complexes of a new L28:hydrazone derived from the condensation of isatin and 2-aminobenzoylhydrazidewith Co (II) and octahedral geometry C30 [17] were synthesized and tested for anticancer activity. The proposed structure of C30 among with the suggested structure of C29 is depicted in figure 8.

Finally, it has to be mention this year's bibliography for biological active Co (II)/(III) complexes. Coordination compounds with cobalt (II) and the ligand 2,6-bis(2,6-diethylphenyliminomethyl)pyridine L29: synthesized and fully characterized. They study its activity using it as anti-proliferative drugs against different human cancer cell lines [18]. The tridentate ligand forms heptacoordinated compound from nitrate metallic salt, where the nitrate acts in a chelating form to complete the seven coordination positionsC31 (figure 9). Two isostructural mononuclear cobalt(III) complexes C32:NO_3•3H_2O and C33:NO_3•CH_3CO_2H•H_2O {[1]+ = [Co(1,10-phenanthroline)2Cl_2]+}, synthesized according to the procedure showing in figure 10 and characterized by x-ray crystallography (figure 11), by addition of 1,10-phenanthroline to a solution of $CoCl_2$•6H_2O followed by the addition of solid CAN (ceric ammonium nitrate) in aqueous acetic acid solution (v/v) at different pH for both complexes at room temperature, respectively [19]. The single crystal X-ray diffraction analysis reveals that both the crystal lattices of C32 and C33 are consisted by identically mono nuclear cationic units [Co(phen)2Cl_2]+ with the only difference that the second one includes solvent molecules. The coordination geometry around each (III) center is best described as distorted octahedron with a CoN_4Cl_2 chromophore. The coordination includes two coordinated phenanthroline ligands, along with two coordinated Cl atoms in mutual orientation in C32 and C33.

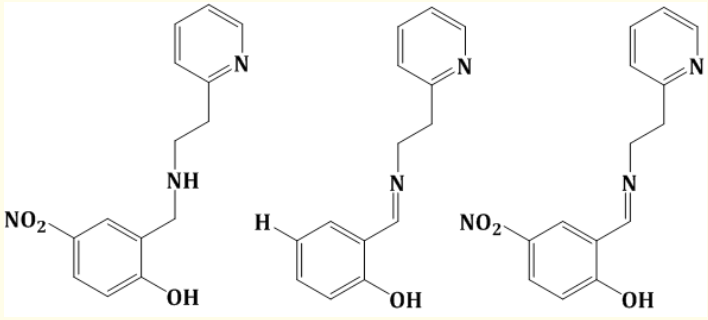

Figure 1: *Shapes of ligands L1, L2, L3 [2].*

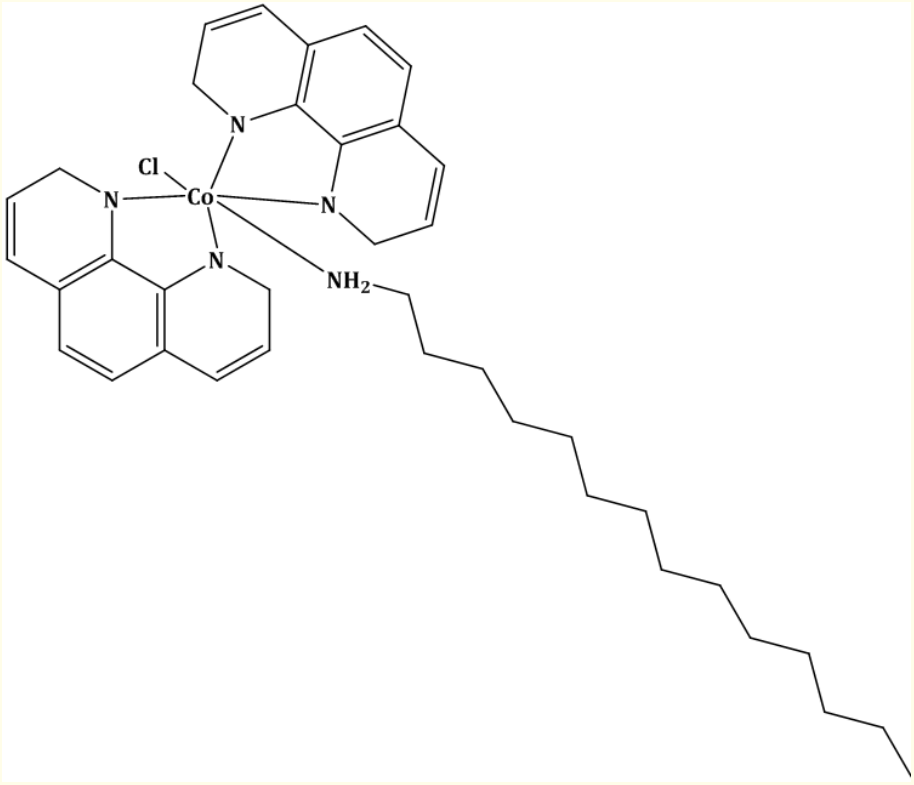

Figure 2: *Shape of molecule C4metallosurfactant with the hydrophilic head and the hydrophobic tail [3].*

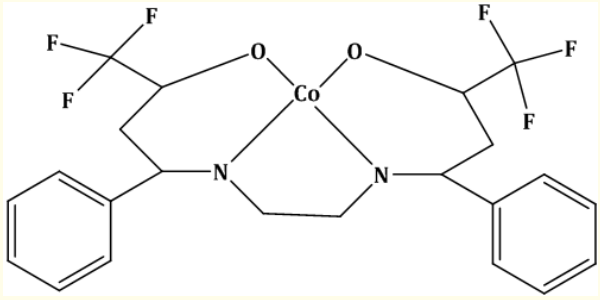

Figure 3: *Molecular structure of C8 [4].*

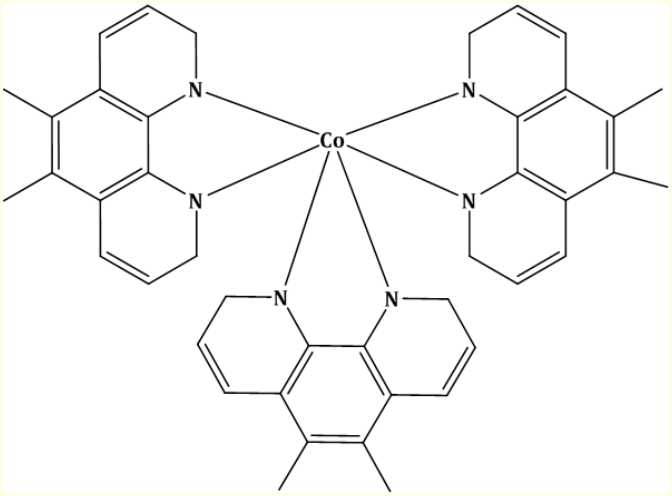

Figure 4: *Molecular structure of C10 [5].*

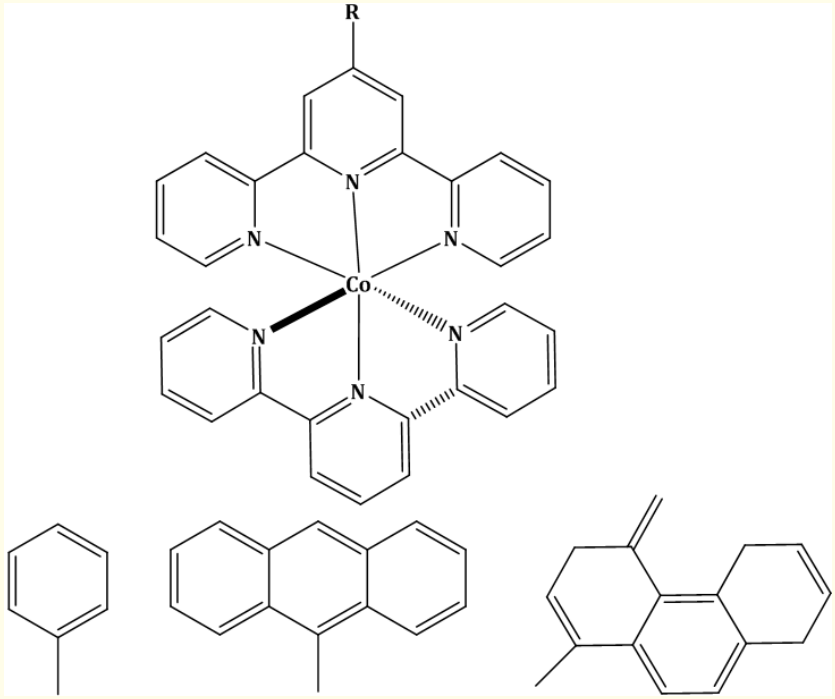

Figure 5: *The ligands L13, L14, L15(down raw)and the complexes C12, C13 and C14 (R group) [7].*

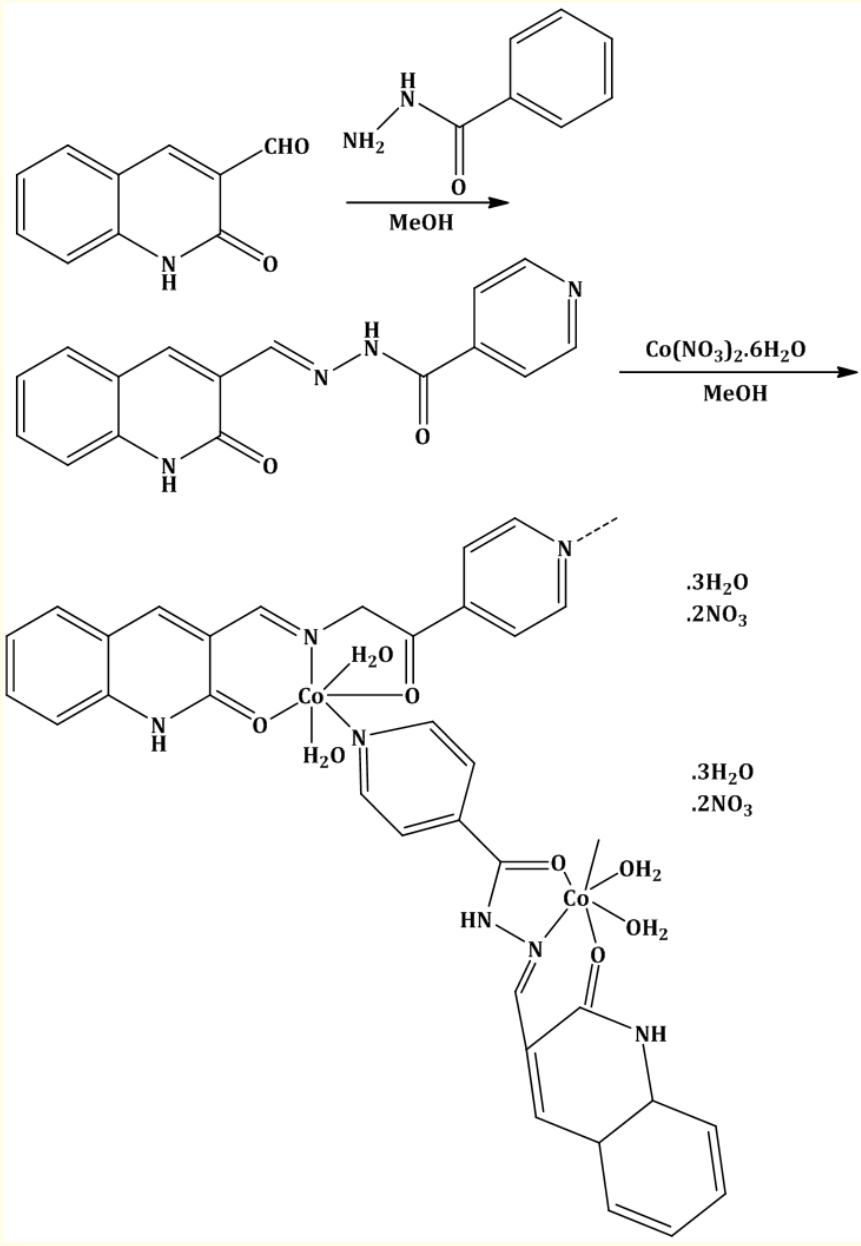

Figure 6: *Preparation routes to the ligand and the complex C20 [9].*

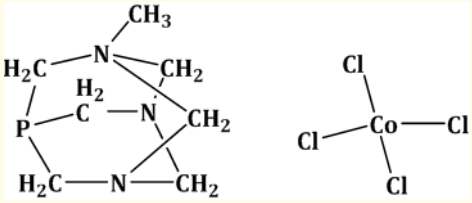

Figure 7: *Coordination scheme of C21 [10].*

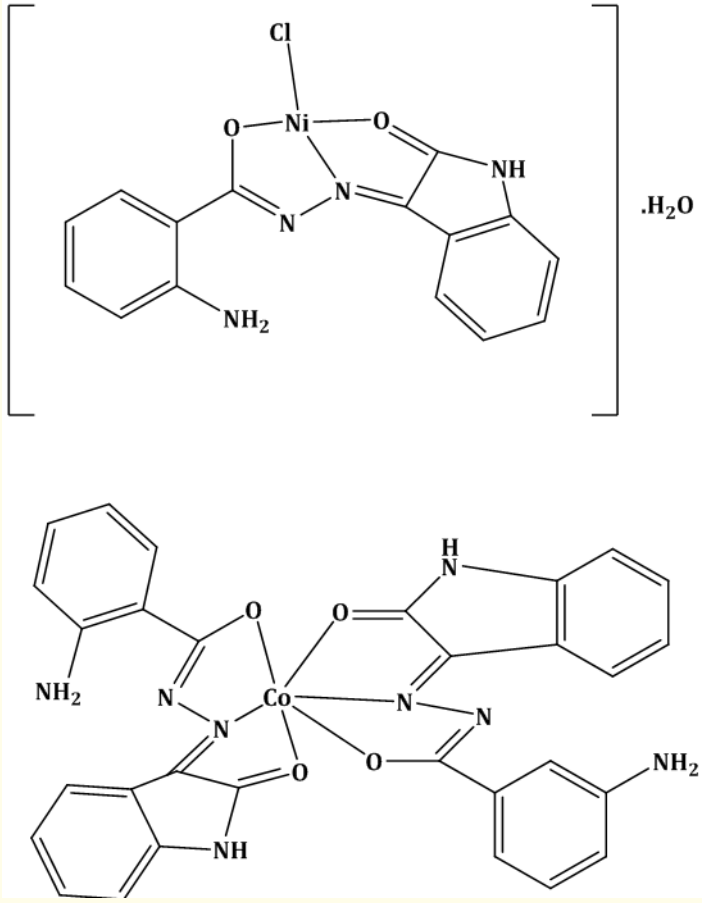

Figure 8: *Proposed structure of C30 along with the suggested of C29 [16].*

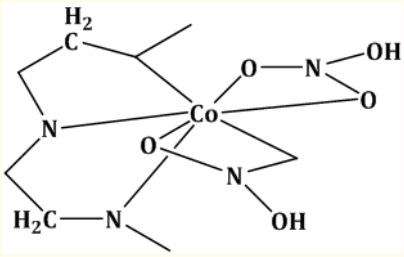

Figure 9: *Coordination sphere of C31 [17].*

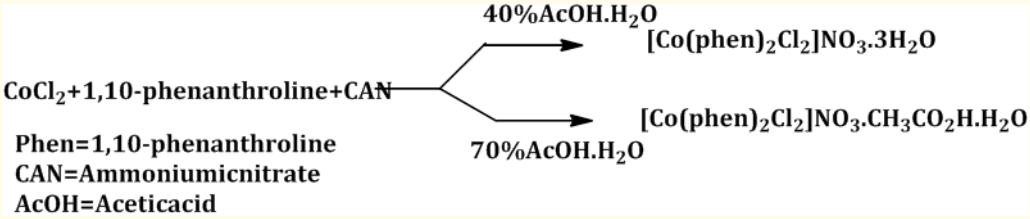

Figure 10: *Synthetic routes of C32 and C33 [18].*

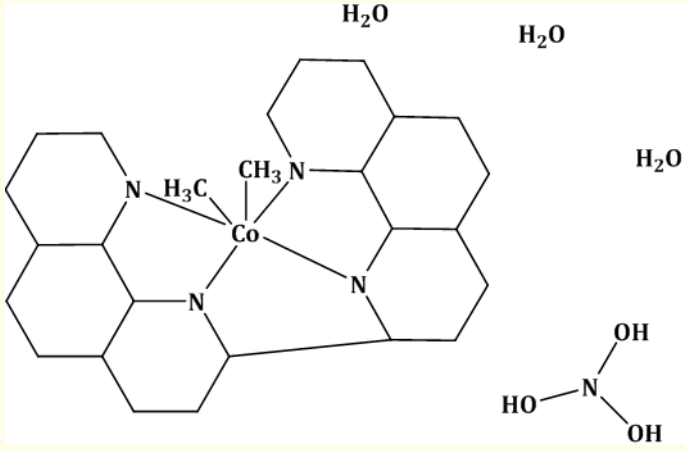

Figure 11: *Coordination sphere of complex C33 [18].*

Anticancer Activity of Cobalt Complexes

The cytotoxicity against tumor cell line was tested on B16F10 cells for the L1, L2, L3, C1, C2 and C3 molecules. In general there was a very low activity of ligand molecules L1, L2 and L3. In opposite the coordinated compounds C1, C2 and C3 enhance the activity due to the Co (III) coordination. C2 and C3 decreased the cell viability at 65% and 25% respectively. The cell killing effects of L1-L3, can be attributed to the coordination of the ligands to Co (III). The observed in vitro cytotoxicity may be related to some oxidative cell damage as well as to structural aspects to the cobalt species [2]. Cytotoxic activity of C4 was examined on cultured Me-180 human cervical cancer cell lines by exposing cells for 24 and 48h to the complex using MTT assay. C4 showed high cytotoxic activity against a cervical cancer cell. This effect could be due to its amphiphilic nature by which they have the capacity to penetrate the cell membrane easily

reduce the energy status of tumors causing activation of lipid peroxidation and DNA damage [3]. Also, the nature of axial ligands could be responsible for the cellular damage. The antitumor screening studies of C5 was applied on SW 620 (human colon carcinoma cell line), Hela (human cervix cancer cell line), Hep G2 (human hepatoma carcinoma cell line), MDA-MB-435 (human breast carcinoma cell line) and A549 (human lung cancer cell line) [4]. In Hep G2 cells, the complex indicated at least three times more effectiveness than that of the ligand L6. On cell lines, SW 620 and MDA-MB-435 the C5 gave very low activity.L8, L9, L10 ligands among with their complexes C7, C8 and C9,were tested in PC-3 prostate cancer cell-line [5]. The viability of cells was assessed by MTT and LDH assay. The Cytotoxic effects of the compounds varied between 12% and 94%. Cobalt complexes are more active than their corresponding ligands. These complexes exhibit concentration - dependent activity against particular cells. In the majority of experiments, the above ligands did not exhibit any significant activity and where they did, it was weaker than that of their corresponding cobalt complexes. In particular C7, could be useful as an antitumor agent and the activity is selective towards prostate cancer and leukemia cells. Some mechanisms that suggested the activity of these complexes includes caspase-3 and MAP kinase activation as well oxidative stress. Regarding the C9, C10 and C11 complexes, C10, rac-[Co(5,6-dmp)3]2+ is remarkable in displaying a cytotoxicity against human breast cancer (MCF-7) cell line more potent than the phen and dpq analogues, which is consistent with its ability to cause changes in the secondary structure of DNA and enhanced cytotoxicity [6]. C13 and C14 showed significant effect in cervical cancer cells. Especially the photo cytotoxicity C14 activity is comparable to the dark toxicity of Cisplatin, while the cobalt (II) complex is non-toxic in the dark. The photo cytotoxicity of C14 is also comparable to the IC50 value of Photofrin [7]. The Cytotoxic effect of C15 among with its ligand L15 was tested in human epithelial breast cancer (MDA-361), human cervical carcinoma (Hela), murine melanoma (B16), and human leukemia cells (K562), human endothelial cells (EA.hy926) and human lung fibroblast (MRC 5) [8]. Table 1 indicates the IC50 values (μM), in different cell lines for the ligand and the complex showing Cytotoxic potential for the coordinated compound.

Investigated Compounds	Cell Lines					
	EA.hy926	MDA-361	He La	MRC 5	K562	B16
$[Co_2L_2]^{2+}$	258	50.9	> 100	> 300	> 100	221
H_2L	124	> 100	72.6	107	> 100	36.8
$Co(NO_3)_2 \bullet 6H_2O$	108	> 100	> 100	222	62.1	139

Table 1: *IC_{50} values (μM) obtained with different cell lines for L16 and C15.*

The complexes C16, C17 and C18 with the clotrimazole as biological active ligand were tested against Hela, PC3 and HCT-15 cell lines showing synergistic anticancer effect comparable with Cisplatin [9]. C19 showed anticancer activity although smaller than that of Cisplatin [10]. Interestingly the C20 molecule exhibited good Cytotoxic activity against Hela, HEp-2, Hep G2 and A431 cancer cell lines without significantly affecting the normal NIH3T3 cells [11]. Regarding the activity of C21 and C22 molecules, C22 is very promising with high specificity against colorectal carcinoma cells [12]. For each ligand, L22 and L23 and their derivatives, C23 and C24 antiproliferative effects against HL-60 cells were exhibited and the associated IC50 values ranged from 5 μM to 20 μM. Furthermore, L22 and its complex C23 inhibited the proliferation of HL-60 cells more effectively than L23, exhibited the strongest anti proliferative activity [13]. The two complexes C25 and C26 inhibit the cell growth of human lung carcinoma cells (A549 cells), human colorectal carcinoma cells (COLO 205 cells), human hepato cellular carcinoma cells (PLC5 cells) and human fibroblast cells (NIH3T3) [14]. C26 shows a higher inhibitory activity, with 46.00 μM IC50 in human colorectal carcinoma cells (COLO 205 cells).

The *in vitro* cytotoxicity has been tested against the human lung adeno carcinoma cell line A-549, Cisplatin-resistant cell line A-549/CDDP and human breast adeno carcinoma cell line MCF-7. Complex C28 is more Cytotoxic than complex C27, and both of themes show higher cytotoxicity than the parent ligands alone L25 and L26. Compared with Cisplatin, the two cobalt (II)complexes are more active against A-549/CDDP and MCF-7 cell lines at most experimental concentrations. Notably, although complex C28 is found to be less effective than Cisplatin against the parent cell line A-549, it is much more effective than Cisplatin against the resistant cell A-549/CDDP

[15]. The complex C29 (IC50 = 2.04–9.7, 2.5–3.7 lg/mL) showed potent antitumor activity comparable with their ligand (IC50 = 11.7, 3.45 lg/mL) against the above mentioned cell lines, respectively. The results evidently show that the activity of the ligand becomes more pronounced and significant when coordinated to the metal ion [16]. Regarding complex C30 it is showed that the IC50 value (32.87 μM) was the second higher of the complex series with the same ligand (L28) [17] as shown in table 2. *In vitro* cell growth inhibition was measured for C31 as well as for the free ligand L29. Upon coordination, the IC50 value of the transition-metal compound is improved compared to the free ligand against colon and prostate cell lines [18].

Finally, regarding molecules C32 and C33, they induce very efficient cleavage of double-stranded DNA without the requirement of activating agents and exhibits important cytotoxicity against human hepato carcinoma cell line (HepG2) in terms of damaging the DNA in cancer cells [19].

Compound	Cell Line/IC50 (μM)			
	HCT-15	PC-3	MCF-7	He La
L27	65.1	130.2	169.0	68.6
$[Co(L)(NO_3)_2]$	45.6	99.9	407.1	79.4
$[Cu(L)(NO_3)_2]$	25.2	38.9	73.9	44.341
$[Zn(L)(NO_3)_2]$	36.8	53.5	394.1	29.8
Cisplatin	< 33.2	38.4	27.3	< 33.2

Table 2: *Cell-growth inhibitory assay results. IC_{50} value after 48h of incubation.*

General Considerations

This mini-review evaluates the work that has been done in the synthesis and characterization of anticancer cobalt molecules and emphasizes only the research works that the structure was totally characterized. It seems from the bibliography that relatively there are very few publications that include the synthesis of cobalt based drugs. So, in my opinion there are a lot of possibilities in this type of research area. In addition to this, it is a mast that every compound is been totally characterized before it is evaluated for its anticancer activity. The structure of a coordinated compound is very important and it is strongly correlated with the grade of the anticancer activity and the specificity that a potential drug shows over particularly cancer cell lines. The activity of cobalt over other transition metals wasn't a target for this review, but it seems that in several times the activity of cobalt ion over a tumor it is overlapped by other transition metals. This fact is not necessary negative because the toxicity of a coordinated compound has to be also mild for the patient. The bet that has to be earned is in the effort for the metal to be transferred in the right place. This is a role that a ligand has to play. The biological activity of the ligand sometimes acts synergistic with the metal, enhancing the anticancer possibility. Other times acts like a vehicle transferring the metal to the tumor. Several novel ligands has to be coordinated with cobalt ions and evaluate for biological activity, but before this happened, the geometry of the complexes should be totally characterized and systematically observed over cancer cell lines because the conformation changes affecting the activity and the specificity of the molecule as well.

Conclusion

In this work, thirty - three coordination compounds of Co (II)/(III) along with twenty - nine ligand molecules that synthesized and in the last five years, were reviewed because of their anticancer activity against several types of human cancer cells. The general clue for this study was that the coordinated cobalt compounds exhibit very higher biological activity than their ligands. It seems to be also a connection between the structure and the specificity of cobalt molecules against cancer cells. Although a relatively low number of cobalt complexes were evaluated for cancer activity in comparison with the ones of Zn, Ni, or Cu, they seems to be promising for future evaluation on further biological studies, in order to be able some of them to be trial on in vivo clinical trials. In my opinion, there is a way in front of us to totally understood the mechanism behind Co (II)/(III) activity. This is the only way to find novel anticancer drugs with lower rates of mortality due to side effects and metastasis.

Acknowledgements

In this stage, I would like to thank the library of the University of Cyprus for its valuable offering research articles.

Conflict of Interest

I declare that neither financial interest nor conflict of interest exists.

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