Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2021, 10 (2): 127-149

(International Peer Reviewed Journal)

Review

Transition Metal Complexes as Therapeutically Relevant Targets for Treatment of Diabetes and Tumor

Pinki and Ashu Chaudhary*

Department of Chemistry, Kurukshetra University, Kurukshetra, Haryana-136119, **INDIA**

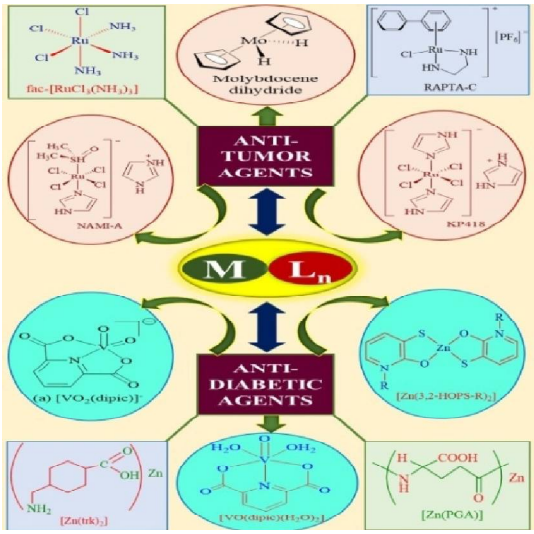
Email: ashuchaudhary21@gmail.com

Accepted on 22nd March, 2021

ABSTRACT

Ongoing revelations in bioinorganic chemistry of potential biomedical significance incorporates the utilization of metal particles as synthetic scaffolds for the planning of small molecule therapeutics. In this review article, we highlight some metal complexes as potential therapeutics for diabetic mellitus and tumor. The complexes used for treatment of diabetic mellitus are of vanadium, zinc, chromium etc. and the complexes having antitumor properties containing metals like platinum, ruthenium, molybdenum, titanium etc.

Graphical Abstract



Keywords: Anti-diabetic agents, Anti-tumor agents, Vanadium, Zinc, Ruthenium, Chromium.

INTRODUCTION

Revelations in inorganic and bioinorganic chemistry have significantly affected current clinical medication. These revelations have dominatingly risen as either metal-containing diagnostic operators

or metal-containing therapeutics [1]. Medicinal inorganic chemistry is a genuinely ongoing branch of bioinorganic chemistry, itself a science still with a lot to learn. It is at the interface among medication and inorganic chemistry, and incorporates metal-based medications, metal sequestering or assembling specialists, metal-containing diagnostic guides, and the medicinal enrolment of endogenous metal particles. Today, therapeutic uses of inorganic chemistry in medication are fluctuated, enveloping numerous parts of the presentation of metal particles into the body (or their intentional evacuation) for remedial or diagnostic impact [2]. In the domain of metal-containing therapeutics, the most conspicuous revelation is that of cisplatin (cis-diamminedichloroplatinum(II), cis-DDP) [3], which is one of the most broadly utilized anticancer medications. The accomplishment of cisplatin can be viewed as especially prominent on the grounds that: (i) the medication is genuinely inorganic, containing no carbon particles (in spite of the fact that the clinically utilized simple carboplatin contains carbon), and (ii) the compound has adequately restored in any event one kind of malignant growth (testicular disease). Notwithstanding cisplatin, another metal-subordinate therapeutics have seen shifting degrees of clinical achievement, including complexes containing gold [4], lithium [5], and iron [6]. In 1999, a topical issue of Chemical Reviews entitled Medicinal Inorganic Chemistry' gave a broad review of numerous subjects in this field of study [7]. Notwithstanding the clinically endorsed employments of metal containing compounds pronounced over, various examinations have been performed and are continuous for recognizing new therapeutic agents from all through the periodic table.

Vanadium compounds have been broadly read for use as insulin mimetics for treatment of diabetic mellitus [8], while metallocene structures and dinuclear rhodium building blocks have been researched as chemotherapeutics for diseases, for example, malignant growth [9]. The role of bioinorganic chemistry in both the improvement of medicinal specialists and in the comprehension of the basic mechanism of ailment unmistakably demonstrates that the field of 'metals in medicines' will keep on making commitments to progressions in human wellbeing in the 21st century. The models gave are not the slightest bit intended to be far reaching or fundamentally reflect even the most critical new revelations; however, they were chosen by the writer/author to feature some imaginative work that is moderately unexplored, yet may have the potential for impressively affecting the eventual fate of the field. Today bioinorganic chemistry is to a great extent an investigation of particles containing metal ions and their molecular interactions by a huge number of strategies and with a wide scope of repercussions. This article deals with various metal complexes which are beneficial for humans in the treatment of diabetic mellitus and tumor.

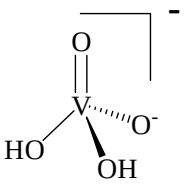
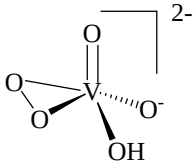
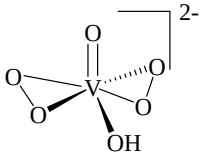
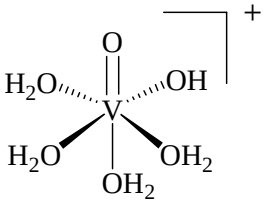
Metal Complexes as Anti-Diabetic Agents: More than 2-8% of total populace is experiencing diabetes [10]. It is a condition where body don't deliver a hormone called insulin which is vital for the ingestion of glucose in cells [11]. Researchers are searching for elective methodologies for the treatment of diabetic mellitus [12]. Diabetes mellitus (DM), which creates numerous auxiliary intricacies, for example, atherosclerosis, microangiopathy, renal dysfunction and disappointment, heart variation from the norm, diabetes retinopathy and visual issues, is named either insulin-subordinate sort 1 or non-insulin-subordinate sort 2, by the WHO. Albeit a few sorts of insulin arrangements for type 1 DM and those of manufactured medications for type 2 DM have been formed and clinically utilized, they have a few issues, for example, physical and mental discomfort because of every day insulin infusions and deformities including side effects, separately.

In the 21st century, another class of pharmaceuticals ought to be presented as various medications are going off patent. Consequently, metallo pharmaceuticals containing vanadium and zinc particles are required to treat the two kinds of DM, by utilizing interesting attributes of the metals [13]. Notwithstanding the therapeutic impact of vanadium particle (Va^{+}) and vanadium building blocks, these vanadium complexes preventively affect the beginning of streptozocin STZ-induced diabetes as far as nitric oxide discharged from the macrophages [14]. In this manner, vanadium is relied upon not exclusively to treat DM however to avoid DM. Notwithstanding vanadium building blocks, zinc complexes have been proposed to be the new applicants in treating type 2 DM. Many metal building

blocks have been arranged and measured to overcome the issues of excruciating insulin infusion and side-effects for type 1/type 2 diabetes mellitus (DM). In spite of the fact that, chromium [15], manganese [16], molybdenum [17], copper [18], cobalt [19], zinc [20] and vanadium particles [21] have been accounted for to show insulin-mimetic or upgrading properties in vitro and in vivo, vanadium is by all accounts the most encouraging one, particularly when coordinated to certain organic ligands.

The revelation, in 1985, that a basic vanadium salt, sodium orthovanadate, added to drinking water, could switch the greater part of the diabetic symptomatology of tentatively diabetic rodents, was exceptionally alluring [22]. Vanadium containing compounds have indicated significant guarantee as orally accessible prodrugs that mitigate the vast majority of the manifestations of diabetes: high glucose, raised lipid levels, and progressively damaging secondary entanglements, including coronary illness, cataracts, kidney disorder and frontier neuropathy [23]. A pivotal advance being developed of vanadium compounds for treatment of diabetic mellitus was the revelation that alteration of the vanadium center by chelation could improve biodistribution and decency [24]. BMOV is the first of various complexes that exhibited better activity over inorganic vanadium sources (for example $VOSO_4$ or $NaVO_3$) through both in vivo as well as in vitro examines of biological viability [25, 26].

Table 1. Insulin-mimetic behavior exhibited by some inorganic vanadium compounds.

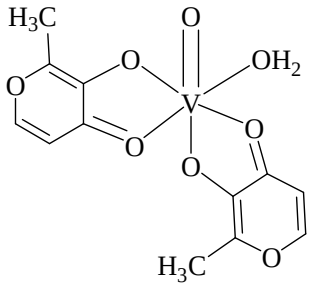
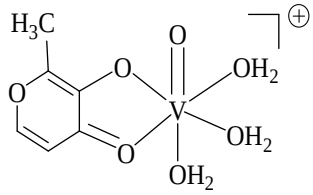
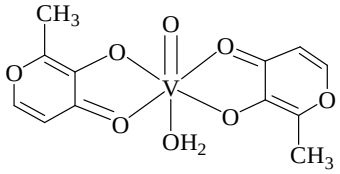
S. No.	Compound type	Compound structure
1.	Orthovanadate	 (a)
2.	Peroxidovanadates	 (b)
		 (c)
3.	Hydrated Oxidovanadium (IV)	 (c)

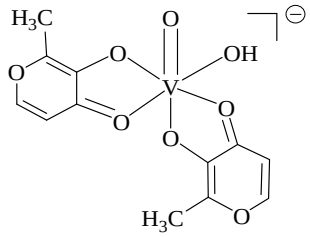
The primary human clinical preliminary was finished as of late of a planned vanadium-based antidiabetic prodrug, bis(ethylmaltolato)oxovanadium(IV) (BEOV), the ethylmaltol analogue of BMOV [27]. The general target of this Phase I preliminary, completed by Medeval Ltd. in Manchester, UK, was to evaluate the security and bearableness of BEOV. Explicit destinations were to: (1) survey the wellbeing impacts of single, escalating doses of orally regulated BEOV; (2) decide

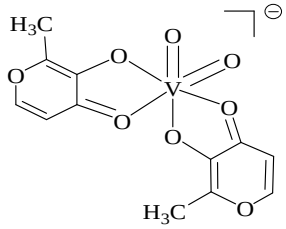
the pharmacokinetics of humble dosages of BEOV from estimated plasma, urinary and fecal [V] absolute; (3) think about the bioavailability of a very much endured portion of oral BEOV and an equivalent molar doses of oral $VOSO_4$; and (4) look at take-up in the fasted, contrasted with the fed, state. Vanadium aggravates that show insulin-like impacts are frequently named insulin mimetics or, maybe more correctly (since even in streptozotocin [STZ]-induced diabetic rodents, there is some leftover insulin formation), insulin-enhancing compounds. In the traditional treatment of diabetic animals and, inconsistently, human people, inorganic vanadium building blocks, for example, vanadate(V), peroxidovanadates(V) and vanadyl sulfate (oxidovanadium(IV)sulfate)have been utilized as shown in table 1. Utilization of vanadate in a dark tea decoction has as of late been exhibited to apply hypo glycemic impacts in a long-term organization to STZ-induced diabetic rodents without apparent harmful reactions [**28**].

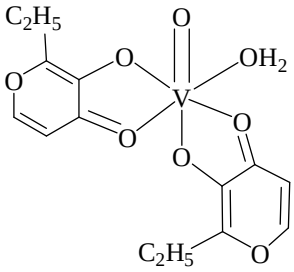
Beginning roughly two decades ago, vanadium building blocks conveying organic ligands in the coordination sphere of the VO^+, VO^{2+} or VO_2^+ cation turned out to be progressively investigated for their antidiabetic potential. A key compound in such manner is $[VO(maltol)_2] \equiv$ BMOV [24,29], (1) in table 2, and subsidiaries thereof, for example, the complexes designed with ethylmaltol (BEOV), (6) [**30**] and allixin (7) [**31, 32**]. The related complex with kojic acid (8; table 2) is a possible candidate in the treatment of diabetes; the particularly stable pyridinone complex 9 in table 2 has been appeared to diminish free unsaturated fat levels [**33**]. Maltol (= 3-hydroxy-2-methyl-pyran-4-one)is a naturally occurring compound present in, for instance, roasted malt, a confirmed food added substance in numerous nations. BMOV and, all the more as of late, BEOV have so far been the main vanadium complexes to be exposed to clinical tests [**30**]. In aqueous arrangement, BMOV experiences speciation to form $[VO(maltol)]^+$, cis-and (to some extent)trans-$[VO(maltol)_2(H_2O)]$ and $[VO(maltol)_2OH]$-table 2 [**34**]. Under toxic conditions, $[VO_2(maltol)_2(H_2O]$ is likewise generated. The oxidovanadium complex designed with allixin is especially active when directed to STZ-instigated diabetic mice [**31**]. Allixin is a constituent of garlic (Allium sativum). Kojic acid, present in parasites, for example, *Aspergillus oryzae* is utilized to mature soybeans.

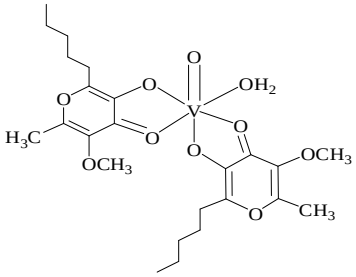
Table 2. Potential antidiabetic complexes related to BMOV and BEOV.

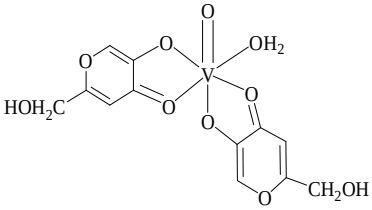
S. No.	Compound Name	Compound Structure
1.	cis-$[V^{IV}O(maltol)_2H_2O]$	
2.	cis-$[V^{IV}O(maltol)(H_2O)_3]^-$	
3.	trans-$[V^{IV}O(maltol)_2H_2O]$	

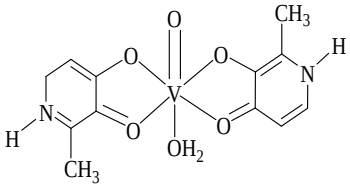
4. cis-[$V^{IV}O(maltol)_2OH]^-$ 

5. cis-[$V^{IV}O_2(maltol)_2$] 

6. [VO(ethylmaltolate)$_2H_2O$] 

7. [VO(allixinate)$_2H_2O$] 

8. [VO(kojicate)$_2H_2O$] 

9. [VO(pyridinone)$_2H_2O$] 

An abundance of vanadium building blocks with vanadium basically in the oxidation states IV and V have been tried, both for their capacity to bring down the blood glucose level and smother lipolysis, with cell cultures (in vitro)and with diabetic creatures (in vivo), for example, STZ rats and Zucker rats as models for diabetes 1 and 2, separately. A choice of promising compounds with O,N-functional ligands is given in table 3. Table 4 sums up results from antidiabetic examinations with vanadate and compounds 1–9.

Table 3. Some oxidovanadium complexes of O, N-functional ligands, with an antidiabetic potential in test animals and/or cell cultures.pic: Picolinate; Trp: Tryptophane; glysal: Salicylglycine.

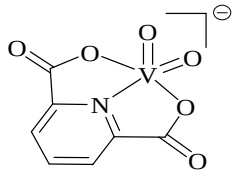
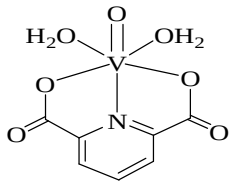
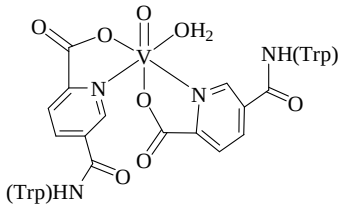
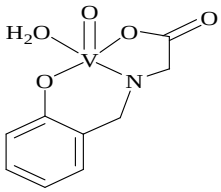
S. No.	Compound Name	Compound Structure
1.	$[VO_2(dipic)]^-$	
2.	$[VO(dipic)(H_2O)_2]$	
3.	$[VO(5TrpNH\text{-}dipic)H_2O]$	
4.	$[VO(glysal)H_2O]$	

Table 4. Some selected vanadium complexes which shows insulin like effects.

S. No.	Ligand	Complex Name	Target	Mode of application	Antidiabetic effect	Ref.
1.	Vanadate in black tea		STZ-diabetic rats	oral administration	Normalization of the blood glucose level; no liver and kidney dysfunction	[28]
2.	Ethylmaltol	$[VO(ethylmaltolate)_2H_2O]$	Phase IIa clinical trials	oral administration	Reduction of fasting blood glucose and glycohemoglobin	[31]
3.	Allixin	$[VO(allixinate)_2H_2O]$	STZ-diabetic mice	oral administration	Lowering of blood glucose level; enhanced phosphorylation of Akt and GSK3b	[32]
4.	Allixin	$[VO(allixinate)_2H_2O]$	STZ-diabetic mice	Intraperitoneal	Lowering of the blood glucose level	[33]
5.	Pyridinone	$[VO(pyridinone)_2H_2O]$	Rat adipocytes		Lowering of the level of free fatty acids	[34]
6.	1, 6-dipicolinic acid	$[VO_2(dipic)]^-$	STZ-diabetic rats	oral administration	Lowering of blood glucose; no significant lowering of serum lipid levels	[143]
7.	1, 6-dipicolinic acid	$[VO(dipic)(H_2O)_2]$	STZ-diabetic rats	oral administration	Lowering of blood glucose; no significant lowering of serum lipid levels	[143]
8.	1,5-dipicolinic acid amide	$[VO(5TrpNH\text{-}dipic)H_2O]$	Rat adipocytes		Inhibition of lipolysis; stimulation of lipogenesis	[144]
9.	Salicylglycine	$[VO(glysal)H_2O]$	Rat adipose tissue		Phosphorylation of Akt	[145]

STZ has been utilized widely to create an exploratory creature model of diabetes since it is specifically harmful to β cells in the pancreatic islets. The i.p. injection of oxidovanadium (IV) sulfate alone (Group III: 283.51 ± 9.21 mg dL^{-1}) and the oxidovanadium (IV)- orotate complex (Figure 1) (Group IV: 410.23 ± 14.52 mg dL^{-1}) both essentially diminished blood glucose levels comparative with the STZ-treated positive control (Group II: 273.77 ± 5.11 mg dL^{-1}). This impact was marginally more articulated in Group IV than in Group III. In accordance with our outcomes, numerous investigations have demonstrated that the organization of vanadate or oxidovanadium (IV) basically standardizes the pathological impacts of STZ treatment in this way re-establishing normoglycemia [**35**].

The health control creatures had fundamentally higher insulin levels than their diabetic partners (Group I: 57.64 ± 1.76 IU mL^{-1}, Group II 23.78 ± 2.50 IU mL^{-1}).These untreated diabetic creatures had essentially less insulin than those treated for 30 days with either oxidovanadium (IV) sulfate alone (Group III: 41.44 ± 1.23IU mL^{-1}) or the oxidovanadium (IV)- orotate complex (Group IV: 42.67 ± 1.77 IU mL^{-1}).These discoveries bolster reports in the writing that oxidovanadium(IV) salts can mimic a considerable lot of the metabolic activities of insulin both in vitro and in vivo and improve the glycemic control that is deficient in diabetes [**36-38**].

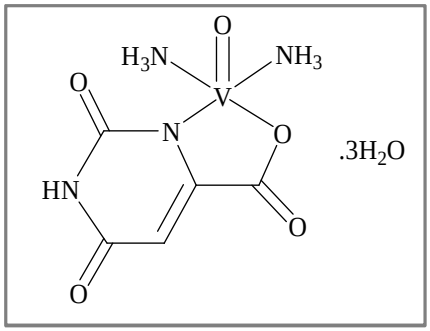


Figure 1. Diammine-orotato-oxidovanadium (IV) complex.

During the troublesome quest for new pharmaceutics, a few metal particles and their building blocks were found to apply antidiabetic impacts in in-vitro and in-vivo frameworks [**30, 39**]. Recently, examines utilizing diabetic animal models like rats and mice just as human diabetic patients have reliably detailed an expanding urinary discharge of zinc in diabetic subjects when contrasted with controls [**40-42**]. Consequently, it was perceived that zinc is a basic factor.

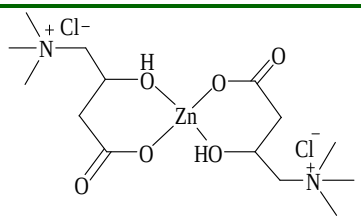
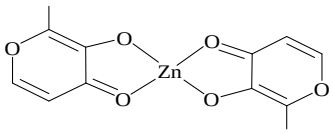
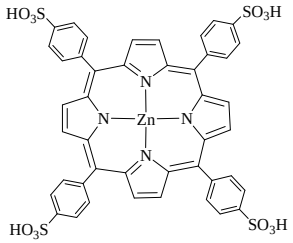
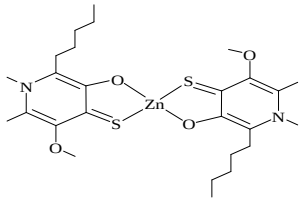
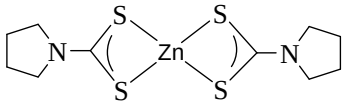
In 1980, similar to insulin, zinc was likewise found to invigorate adipocyte lipogenesis in rats [**43**]. Afterward, oral administration of $ZnCl_2$ was found to apply in vivo antidiabetic impacts in STZ-rats and ob/ob mice in 1992 [**44**] and 1998 [**45**], separately. In 2001, Simon et al. announced that dietary zinc supplementation diminished high blood glucose levels in db/db mice [**46**], yet the administration portions were high, i.e., over the median lethal dose (LD50) esteem. The bioavailability of $ZnCl_2$ is moderately low, and along these lines the complexation of zinc was endeavoured.

Sakurai *et al* and Kojima *et al* respectively have proposed a wide assortment of zinc(II) complexes with various coordination modes, for example, $Zn(N_2O_2)$, $Zn(O_4)$, $Zn(S_2O_2)$, $Zn(N_4)$, and $Zn(S_4)$ [**47-49**]. Bis(picolinato)Zn ($[Zn(pa)_2]$) and bis(amino acidato)Zn building blocks are instances of complexes with the $Zn(N_2O_2)$ coordination mode [**50**]. In an examination completed in 2001, bis(maltolato)Zn ($[Zn(ma)_2]$), a complex with the $Zn(O_4)$ coordination mode, was found to show high antidiabetic activity after intraperitoneal (i.p.) injection in KKAy mice [**51**]. They examined the structure-action connections of its related building blocks and proposed bis(3-hydroxy-5-methoxy-9-methyl-2-penthyl-4H-pyrane-4-one; allixin)Zn, a complex with the $Zn(O_4)$ coordination mode. This complex has high insulinomimetic action in vitro frameworks [**52**].

In addition, after the in vitro assessment of a few prepared complexes, the bis(S-allixinato-N-methyl)Zn ([Zn(sanm)$_2$]) complex with the Zn(S_2O_2) coordination mode was seen as the best and showed a 20-fold higher concealment of free unsaturated fat release in adipocytes than did the [Zn(ma)$_2$] complex [**52**]. Simultaneously, we integrated zinc complexes with the Zn(N_4) coordination mode, e.g., bis(2-aminomethylpyridinato)Zn ([Zn(2-ampy)$_2$]), bis(2-aminoethylpyridinato)Zn ([Zn(2-aepy)$_2$]), and (1,5,8,12-tetraazadodecanato)Zn([Zn(1,5,8,12-td)]) building blocks [**53**].

Among these complexes, i.p. injections of [Zn(2-ampy)$_2$] were found to bring down blood glucose levels in KKAy mice. As of late, Saha et al. revealed that the water-dissolvable Znporphyrin complex (meso-tetrakis(4-sulfonatophenyl)porphyrinato) Zn ([Zn(tpps)]), in which Zn(N_4) is the zinc coordination circle, applied insulinomimetic exercises when presented by oral gavage in KKAy mice [**54**]. Table 5 shows the structures of orally active antidiabetic zinc building blocks with various coordination conditions [**54-58**]. Among these complexes, bis(pyrrolidine-N-dithiocarbamato)Zn ([Zn(pdc)$_2$]) with the Zn(S_4) coordination mode applied incredibly high hypoglycemic impacts in KKAy mice when managed orally [**56**]. Furthermore, hemoglobin A1c (HbA1c) levels were improved, and serum boundaries that are demonstrative of insulin resistance likewise were improved in the wake of administering [Zn(pdc)$_2$] for 25 days. Insulin resistance is considered to assume a focal role in the advancement of a scope of metabolic issues. The control KKAy mice directed the vehicle alone had serious hyperinsulinemia, hypertriglyceridemia, hypoadiponectinemia and hyperleptinemia.

Table 5. Structures of Orally Active Zn Complexes with Antidiabetic Effect.

S. No.	Complex type	Complex name	Complex structure
1.	O_4 Type	[Zn(car)$_2$]	
2.	O_4 type	[Zn(mal)$_2$]	
3.	N_4 type	[Zn(tpps)]	
4.	S_2O_2 type	[Zn(tanm)$_2$]	
5.	S_4 type	[Zn(pdc)$_2$]	

At the point when we regulated zinc complex, it was emphatically seen to bring down the blood glucose levels. In this way, there is a chance of causing serious hypoglycaemia on the off chance that we unreasonably control the exceptionally bioavailable zinc complex. In this manner, when the zinc complex is directed, it will be essential to set the ideal portion for the protected cure.

Other intriguing antidiabetic zinc complexes have as of late been proposed [**59-66**]. Besides, it has been accounted for that glucose digestion was expanded in GK rats managed Zn/cyclo (His-Pro) [**60**]. Fujimura et al. announced that the bis(tranexamic acidato) Zn complex hindered α-glucosidase and improved diabetic state [**61**]. Katoh *et al*. detailed that zinc complexes with different heterocyclic bidentate ligands have high insulinomimetic action and decreased blood glucose in vivo in KKAy mice [**62**]. Likewise, different zinc building blocks have been proposed recently (Figure 2).

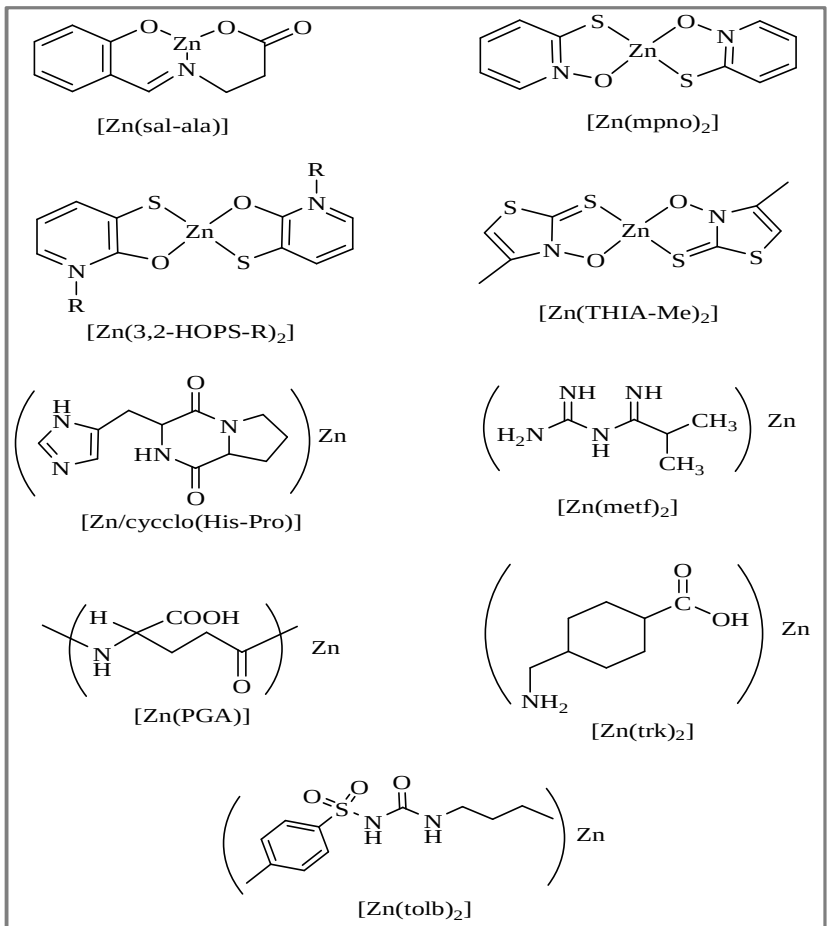


Figure 2. *In Vitro* and *In Vivo* Antidiabetic New Zn Compounds with Various Ligands.

Chromium is a fundamental mineral that is believed to be important for typical glucose and lipid homeostasis [**67**]. Trivalent chromium in a complex known as glucose tolerance factor is viewed as the biologically active form. It was initially found in brewer's yeast [**68**]. Chromium chloride [69], chromium nicotinate [**70**] and chromium picolinate [**71, 72**] are usually formulations of Cr^{3+}. Serious chromium insufficiency is known to cause reversible insulin resistance and diabetic mellitus [**73, 74**].

Studies on chromium histidinate complex as a Cr supplement was seen as reasonable for people that was ingested better than any of those accessible [**75**]. A recently synthesized chromium complex chromium(phenyl alanine)- improves insulin responsiveness and decreases entire body glucose resistance [**76**]. Synthesis, characterization and hypoglycemic activity of Cr^{3+}complexes with gliclazide, glibenciamide and glimeperide oral antidiabetic allopathic drugs have been considered by

Tawkir *et al.* [77]. The impact of Cr(III) complexes (acetic acid derivatives, chloride, glycinate, histidinate, lactate and propionate) on insulin binding and sign transduction was examined by Mackowiak *et al* [78].

Metformin hydrochloride (MF.HCl) (1,1-dimethyl biguanide) is an oral hypoglycemic specialist which is generally endorsed for the treatment of diabetes mellitus type II [79]. There is a lot of enthusiasm for MF ligand and its transition metal complexes which are cationic in nature [80]. As of late, Cr(III)- MF.HCL complex (Figure 3) as a diabetic medication model was incorporated and has prevailing to incredible extent as antidiabetic drug with improved cancer prevention agent defense system just as go about as articulated proficient hypoglycemic agent contrasted with the MF free medication [81].

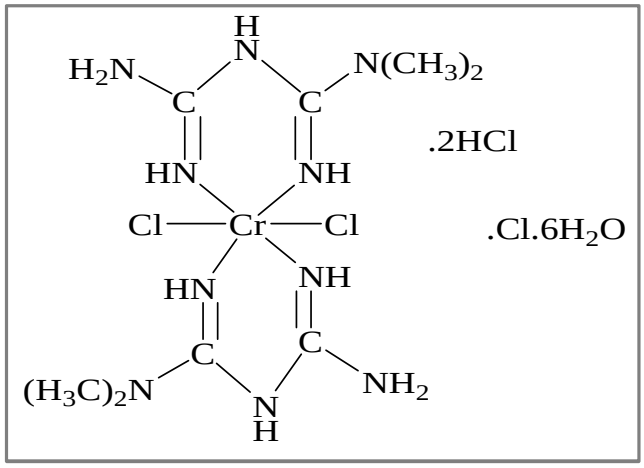
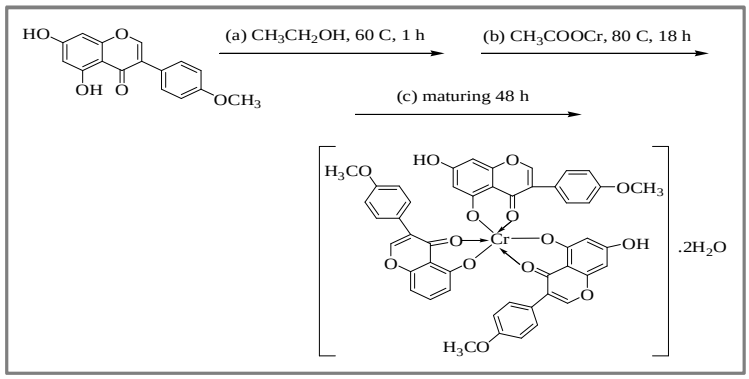


Figure 3. Chromium)III)-metformin hydrochloride complex.

Chromium (Cr^{3+}) is a basic component in the human body and is required for glucose and lipid digestion. Cr^{3+} impacts the structure and capacity of insulin and the status of target tissues and cells essentially. An absence of chromium in the body prompts the dysregulation of glucose and lipid digestion and advances atherosclerosis, diabetes, hyperlipidemia and different side effects. Past examinations had demonstrated that diabetic patients were regularly chromium insufficient. Isoflavones may shape complexes with chromium, which could decrease harmfulness of inorganic chromium and increment the level of absorption [82] in diabetic mellitus patients. This may prompt better hypoglycemic impacts. The synthesis course to subsidiary complex is appeared in scheme 1.



Scheme 1. Synthesis of complex of chromium (+3).

Inorganic Compounds as Anti-Tumor Agents: The clinical accomplishment of cis-diammine dichloroplatinum(II) and its subsidiaries in the treatment of malignancy has enormously affected the disclosure of novel anti-cancer metallo-pharmaceutical agents [83-89]. Cisplatin and carboplatin are

utilized to treat different kinds of malignancies, for example, ovarian, head and neck, lung and bladder malignant growth [**90**]. Oxaliplatin was the primary medication equipped for defeating cisplatin resistance of colon carcinoma [**86**]. Other platinum building blocks for example nedaplatin, lobaplatin or heptaplatin (Figure 1) were provincially endorsed [**86**]. Nonetheless, platinum-based medications have various detriments [**91**]. They are dormant against a few tumors and their general toxicity levels lead to undesirable reactions in cancer patients. Moreover, the drug-resistance marvels likewise bring down the effect of these agents. In this manner, these uncertain impediments animate the exploration on the advancement of novel transition metal complexes containing improved natural ligands [**84, 85, 87, 92-101**].

A non-platinum metal complex that reduces the malignant growth are right now not utilized in the clinic. All things considered, complexes of ruthenium (for example NAMI-A and KP1019, figure 4) [**102, 103**], titanium (for example budotitane and titanocene dichloride, figure 4) [**104, 105**], or gallium (for example gallium nitrate, gallium chloride and gallium maltolate) [**106, 107**] were at that point tried in clinical preliminaries and complexes with for example silver, gold, copper, iron, palladium, osmium, iridium or rhodium as focal particle demonstrated promising outcomes in preclinical investigations [**89, 92-101**].

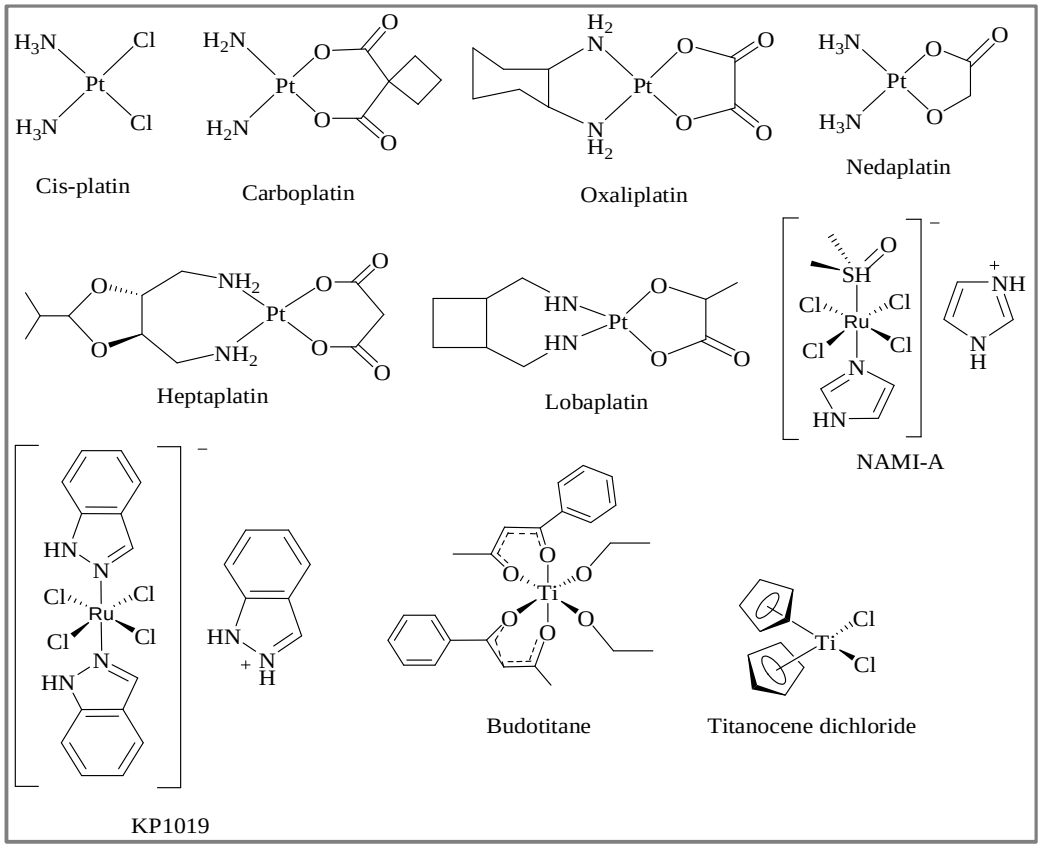


Figure 4. Some platinum-based drugs and non-platinum metal complexes having anti-cancer properties.

During the 1980s, Clarke [**108**] revealed the anticancer action of a Ru (III) complex against essential tumors, yet the complex was not exposed to additionally tests because of poor water solvency (Table 6). A couple of years after the fact, Keppler and associates [**109, 110**] presented a gathering of complexes represented by KP418 and KP1019, containing nitrogen-facilitated heterocyclic ligands in trans-positions, four equatorial chloride ligands and a protonated azole or sodium ion for charge remuneration. Both complexes introduced great anticancer action against colorectal malignant growth cell lines and platinum resistance colorectal autochthonous tumors [**111, 112**].

Regardless of the promising anticancer properties, KP418 didn't experience testing in human preliminaries because of higher nephrotoxicity in murine models in contrast with KP1019. The essential method of activity was proposed to be covalent binding to DNA. KP1019 experiences moderate ligand exchange under physiological conditions, comparably to platinum-based anticancer operators. Further examinations indicated that the Ru particles (from KP1019) were restricted generally in the cytosol and in the nuclear regions [**113**]. Lamentably, KP1019 fizzled in a stage II preliminary, primarily on account of poor water solvency [**114**]. Blood investigation of patients rewarded with KP1019 demonstrated under 1% of the KP1019 portion bound to transferrin, recommending a restricted role for transferrin in drug transport [**115**].

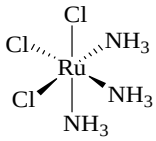
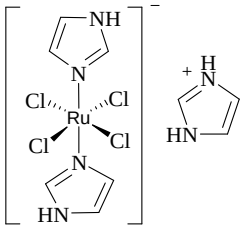
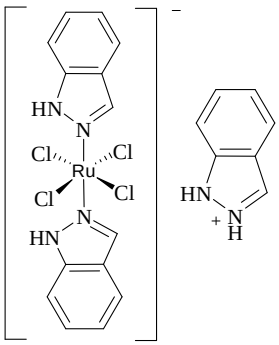
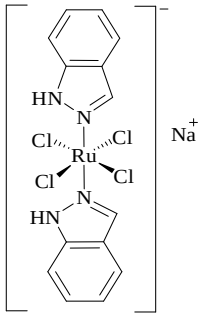
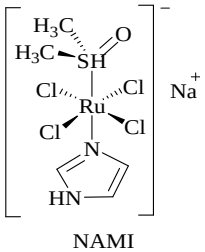
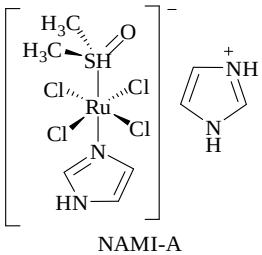
Further exploration has indicated that human serum egg whites promptly binds KP1019 and its analog NKP1339 in plasma, and this blood protein likely assumes anenormousrole in transport and limitation of this class of Ru(III) drugs [**116**]. NKP1339 was acquainted with a sodium particle with improved water solvency, and the cell take-up of NKP1339 is rapid, clarified by the facile response of the Ru(III) complex with serum proteins. While, the specific method of activity of the Ru(III) complexes detailed here is as yet not satisfactory, three conceivable theories have been advanced to clarify the anticancer action of NKP1339: (i) communication with glucose regulated proteins prompting a reduction of the unfolded protein reaction (UPR), (ii) enlistment of the G2/M cell cycle capture and (iii) apoptosis of the malignant growth cells by means of a mitochondrial pathway [**115**].

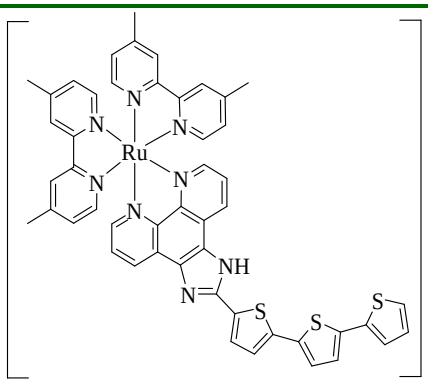
Not long after Keppler, Alessio and Sava with colleagues [**117**] revealed an examination on a practically equivalent to compound to KP418, with one azole ligand replaced by DMSO (NAMI). However, in clinical preliminaries, the imidazolium-compensated analog - NAMI-A was utilized. Testing in the NCl-60 cell line panel, this complex indicated no or much lower cytotoxicity against a few solid tumor cell lines in contrast with cisplatin [**116**]. NAMI-A was progressively successful at repressing the proliferation of chose leukemia cell lines, through blockade of the KCa 3.1 channels [**116**]. At high concentrations of NAMI-A, the anticancer movement included DNA and RNA binding, obstructing the cell cycle movement and the restraint of solid tumor metastasis by association with the cell surface protein [**113, 116**].

At progressively important physiological concentrations of the compound, a diminished capacity of the malignant growth cells to enter into collagen gels, decreased cell motility and expanded cell adhesion were examined [**116**]. Moreover, NAMI-A immobilized a key advance of angiogenesis at micromolar concentrations [**118**]. The antimetastatic action was seen at doses from 100 to multiple times below the cytotoxic dose [**116**]. Analyses performed with the NAMI-A complex within the sight of HSA demonstrated less cytotoxicity, which was clarified by the lower bioavailability of the compound on being bound to HSA. Studies in animal models recorded a synergistic impact of NAMI-A joined with conventional anticancer operators (e.g., 5-fluorouracil [**119**], cisplatin [**120**], doxorubicin [**121**] or gemcitabine [**122**]). Particularly encouraging outcomes were acquired for NAMI-A joined with gemcitabicin in preclinical investigations. Shockingly, during stage II clinical preliminaries, treatment at the maximum tolerated dose (MTD) indicated reduction in just one case and balanced out the malady in ten cases. These outcomes were not agreeable and the examination was suspended.

The latest Ru compound to be gone into clinical preliminaries is TLD-1433 (Table 6), a Ru(II) polypyridyl complex reasonable for PDT applications [**123, 124**]. Combination of TLD-1433 with transferrin (Rutherrin) improves the photophysical properties, pharmacokinetic properties and toxicology, in contrast with TLD-1433 alone [**123**]. Studies performed without light activation or just within the sight of TLD-1433, indicated no proof of action on bladder tumor development, healthy urothelium and bladder musculature [**124**]. After PDT treatment, huge tumor necrosis was observed, with sound cells indicating just nearby aggravation [**125**]. The announced method of activity depends on ROS production, annihilating the mitochondria and initiating cell apoptosis.

Table 6. Timeline of the most intensively studied Ru complexes [**116**].

S. No.	Discovered by	Complex name	Complex structure
1.	Clarke and coworkers (1980)	fac-[$RuCl_3(NH_3)_3$]	
2.	Keppler and coworkers (1986)	KP418 and KP1019	 KP418  KP1019
3.	Keppler and coworkers (1989)	NKP1339	
4.	Alessio, Sava and coworkers (1992)	NAMI and NAMI-A	 NAMI  NAMI-A

5.	McFerkand and coworkers (2017)	TLD1433	

In spite of the set number of Ru compounds entering clinical preliminaries, a lot of other Ru compounds show promising remedial information. A considerable lot of the complexes are minor auxiliary varieties of those as of now explored in clinical preliminaries, for example, NAMI-Pyr (or AziRu) (Figure 5) which is a simple of NAMI-A (Walsby and associates [**126**], Padeuano and collaborators [**127, 128**]). Walsby and collaborators inspected a library of NAMI-A and KP1019 analogs to explore the impact of the axial ligands on the physicochemical properties [**129, 130**]. A class of ruthenium(II) arene building blocks, for example, RAPTA-type complexes, target proteins, while RM175 – type compounds target DNA [**131**] (Figure 5). Ru building blocks have additionally been utilized with peptides (e.g., octreotide), amino acids, steroids, natural product ligands (e.g., curcumin) and purine or nucleoside ligands to improve their therapeutic properties [**132**].

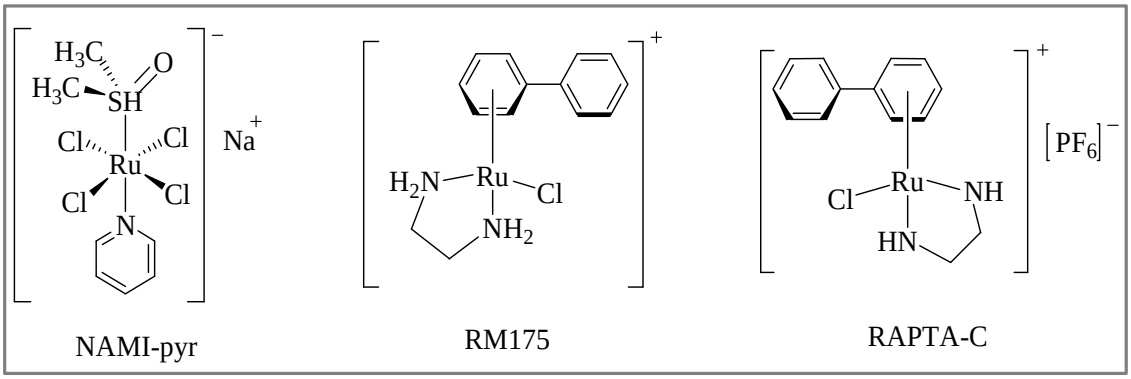


Figure 5. Some Ruthenium compounds as promising therapeutic properties.

The current medicines for malignant growth are surgery, radiation, and chemotherapy. In chemotherapy, certain classifications of significant inorganic complexes molybdenum halides (molybdenum(II) chloride and molybdenum(III) chloride), molybdenum oxides (molybdenum(IV) oxide (MoO_2), and molybdenum(VI) oxide (MoO_3)), iso-and heteropolyoxomolybdates), molybdenum hexacarbonyl and hybrid inorganic-organic materials, and molybdenum oxides (Mo_n−nO_3). They are utilized inconceivably for therapeutic applications [**133, 134**].

Organomolybdenum compounds can be alluded to facilitated molybdenum compounds in different oxidation states. They are intense anticancer and antimicrobial specialists [**134-138**]. As per Nair *et al.*, biological uses of molybdenum building blocks were because of the capacity of consolidated ligands to chelate with trace metal ion (molybdenum particle), their uncommon activity components, and ability to deliver a high measure of harmful reactive oxygen species (ROS) which can intrude on the redox parity of a system prompting increment in deoxyribonucleic acid (DNA) harm, DNA protein cross-linked arrangement, lipid peroxidation, cell toxicity, as well as off-base inception of cell signaling ways [**135**]. Results from their discoveries affirmed that Mo(V) had more cytotoxic exercises than Mo(VI).

On another note, Mel'endez demonstrated that metallocenes are target explicit medications for malignancy treatment. A metallocene is an organometallic compound, which as a rule comprises of two cyclopentadienyl anions bound to a central metal (M) in the oxidation state, to yield $(C_5H_5)_2M$ [**139**]. Ndagi *et al*., [**140**] and Martin *et al*., [**141**] expressed the lower consideration on metallocenes (molybdocene, niobocene, vanadocene, and zirconocene) in context of cytotoxic effects on malignant growth cell lines when contrasted with metal-based compounds. Marin et al. recommended additional streamlining of these metallocenes for them to be utilized as anticancer specialists in chemotherapy [**141**].

Molybdocene is a metallocene with a molybdenum atom. Molybdocene dichloride is the organomolybdenum which has the equation of $(\eta^5\text{-}C_5H_5)_2MoCl_2$ (Figure 6). The International Union of Pure and Applied Chemistry (IUPAC) name is dichlorobismolybdenum(IV). Molybdocene dichloride had been accounted for to show anticancer exercises, yet there was a test of no yield of significant compounds at the clinical stage [**142**]. Other organomolybdenum compounds are molybdocene dihydride, (mesitylene) molybdenum tricarbonyl, and cycloheptatrienenmolybdenum tricarbonyl, as appeared in Figure 6.

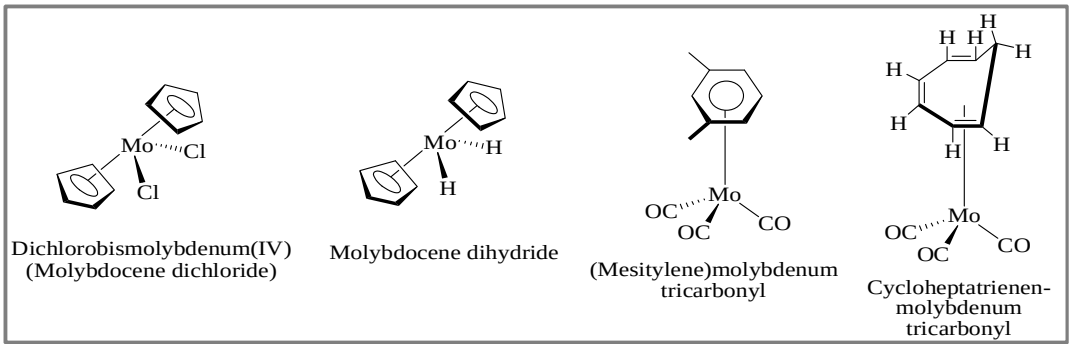


Figure 6. Some metallocenes of molybdenum used in anticancer therapy.

CONCLUSION

It is concluded that there may be indeed a great variety of some antidiabetic and antitumor drugs which provide relief in the symptoms of the diseases and also used for the chemotherapy. To cure people from diabetes and different types of tumor, the metal complexes like BMOV, BEOV, their derivatives, some vanadium complexes containing O, N-functional groups, zinc compounds, chromium compounds can be used clinically to treat diabetic mellitus and complexes of platinum like cisplatin, oxaliplatin, carboplatin, lobaplatin, heptaplatin, nedaplatin etc., complexes of ruthenium like KP418, KP1019, NAMI, NAMI-A, NKP1339, TLD1433, NAMI-pyr, RM175, RAPTA-C etc., titanocene, molybdocene are clinically used to treat tumor. Ongoing research is helpful to improve the therapeutic properties of the different metal complexes.

List of Abbreviations

DMSO: Dimethyl sulfoxide,
DNA: Deoxy-Ribo-nucleic acid,
ROS: Reactive oxygen species,
DM: Diabetic mellitus,
STZ: Streptozotocin,
BEOV: bis(ethylmaltolato)oxovanadium(IV),
Trp: Tryptophane,
LD50: Lethal dose 50,
pdc: bis(pyrrolidine-N-dithiocarbamato,
mpno: 2-mercaptopyridine-*N*-oxide,
RNA: Ribo-nucleic acid,
MTD: Maximum tolerated dose,β,
cis-DPP: cis-diamminedichloroplatinum(II),
WHO: World Health Organisation,
BMOV: bis(maltolato)oxovanadium(IV),
pic: picolinate,
Gly-sal: Salicylglycine,
tpps: meso-tetrakis(4-sulfonatophenyl)porphyrinato
sal-ala: N-salicylidene-β-alanin,
PGA: poly-γ-glutamic acid,

3,2-HOPS: 3-hydroxypyridine-2(1*H*)-thione,
trk: tranexamic acid,
tolb: tolbutamide,
THIA: 3-hydroxy-4-methyl-thiazole-2(3*H*)-thione,
His-Pro: histidyl-proline,
metf: metformin

ACKNOWLEDGEMENT

One of the authors Ms. Pinki wishes to express gratitude to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial assistance in the form of JRF Vide letter no.: 09/105(0308)/2020-EMR-I.

Conflict of Interest: The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

[1]. K. H. Thompson, C. Orvig, Metal complexes in medicinal chemistry: new vistas and challenges in drug design, *Dalton Trans*, **2006**, 14, 761-764.
[2]. P. J. Sadler, Inorganic Chemistry and Drug Design, *Adv. Inorg. Chem.*, **1991**, 36, 1-48.
[3]. E. R. Jamieson, S. J. Lippard, Structure, Recognition, and Processing of Cisplatin−DNA Adducts, *Chem Rev.*, **1999**, 99, 2467-2498.
[4]. C. F. III Shaw, Gold-based therapeutic agents, *Chem Rev.*, **1999**, 99, 2589-2600.
[5]. N.J. Birch, Inorganic pharmacology of lithium, *Chem Rev.*,**1999**, 99, 2659-2682.
[6]. C. A. Claussen, E. C. Long, Nucleic acid recognition by metal complexes of bleomycin, *Chem Rev.*, **1999**, 99, 2797-2816.
[7]. C. Orvig, M. J. Abrams, Medicinal inorganic chemistry: introduction, *Chem Rev.*, **1999**, 99, 2201-2203.
[8]. K. H. Thompson, J. H. McNeill, C. Orvig,Vanadium compounds as insulin mimics, *Chem Rev.*,**1999**, 99, 2561-2571.
[9]. M. J. Clarke, F. Zhu, D. R. Frasca,Non-platinum chemotherapeutic metallopharmaceuticals, *Chem Rev.*, **1999**, 99, 2511-2533.
[10]. S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, *Diabetes Care*, **2004**, 27(5), 1047-1053.
[11]. K. I. Rother, Diabetes Treatment-Bridging the Divide, *The New Engl. J. Med.*, **2007**, 356(15), 1499-1501.
[12]. R. Nahas, M. Moher, Complementary and alternative medicine for the treatment of type 2 diabetes, *Can. Fam. Physician*, **2009**, 55(6), 591-596.
[13]. A. Tsuji, H. Sakurai, Vanadyl Ion Suppresses Nitric Oxide Production from Peritoneal Macrophages of Streptozotocin-Induced Diabetic Mice, *Biochem. Biophys.Res. Commun.*, **1996**, 226(2), 506-511.
[14]. R. Gherji,C. Caratti, G. Andraghetti,S. Bentolini, A. Montemurro, G. Sesti, R. Cordera, Direct modulation of insulin receptor protein tyrosine kinase by vanadate and anti-insulin receptor monoclonal antibodies, *Biochem. Biophys. Res. Commun.*, **1988**, 152(3), 1474-1480.
[15]. S. Yoshimoto, K. Sakamoto,I. Wakabayashi, H. Masui, Effect of chromium administration on glucose tolerance in stroke-prone spontaneously hypertensive rats with streptozotocin-induced diabetes, *Metabolism*,**1992**, 41, 636-642.
[16]. S. Subasinghe, A. L. Greenbaum, P. McLean, The insulin-mimetic action of Mn^{2+}: Involvement of cyclic nucleotides and insulin in the regulation of hepatic hexokinase and glucokinase, *Biochem. Med.*, **1985**, 34(1), 83-92.
[17]. A. T. Ozcelikay, D. J. Becker, L. N. Ongemba, A. M. Pottier, J. C. Henquin, S. M. Brichard, Improvement of glucose and lipid metabolism in diabetic rats treated with molybdate, *Am. J. Physiol.*, **1996**, 270(2), 344-352.

[18]. P. L. Walter, A. Kampkötter, A. Eckers, A. Barthel, D. Schmoll, H. Sies, L. O. Klotz, Modulation of FoxO signaling in human hepatoma cells by exposure to copper or zinc ions, *Archives of Biochemistry and Biophysics.*, **2006**, 454(2), 107-113.
[19]. J. Ybarra, A. Behrooz, A. Gabriel, M. H. Koseoglu, F. Ismail-Beigi, Glycemia-lowering effect of cobalt chloride in the diabetic rat: increased GLUT1 mRNA expression, *Mol. Cell. Endocrinol*., **1997**, 133, 151-160.
[20]. J. M. May, C. S. Contoreggi, The mechanism of the insulin-like effects of ionic zinc, *J. Biol. Chem.*, **1982**, 257(8), 4362-4368.
[21]. H. Sakurai, K. Tsuchiya, M. Nukatsuka, M. Sofue, J. Kawada, Insulin-like effect of vanadyl ion on streptozotocin-induced diabetic rats, *J. Endocrinol*., **1990**, 126(3),451-459.
[22]. C. E. Heyliger, A. G. Tahiliani, J. H. McNeill, Effect of vanadate on elevated blood glucose and depressed cardiac performance of diabetic rats, *Science*, **1985**, 227(4693), 1474-1477.
[23]. A. R. Saltiel, C. R. Kahn, Insulin signalling and the regulation of glucose and lipid metabolism, *Nature*, **2001**, 414, 799-806.
[24]. J .H. McNeill, V. G. Yuen, H. R. Hoveyda, C. Orvig, Bis(maltolato)oxovanadium(IV) is a potent insulin mimic, *J. Med. Chem.*, **1992**, 35(8),1489-1491.
[25]. Y. Shechter, G. Eldberg, A. Shisheva, D. Gefel,N. Sekar, S. Qian, R. Bruck, E. Gershonov, D. C. Crans, Y. Goldwasser, M. Fridkin, J. Li.In Vanadium Compounds. Chemistry, Biochemistry, and Therapeutic Applications, ed. Tracey AS, Crans DC.*ACS Symposium Series 711*, Washington DC, **1998**, 308–315.
[26]. P. Caravan, L. Gelmini, N. Glover, F. G. Herring, H. Li, J. H. McNeill, S. J. Rettig, I. A. Setyawati, E. Shuter, Y. Sun, A. S. Tracey, V. G. Yuen, C. Orvig, Reaction Chemistry of BMOV, Bis(maltolato)oxovanadium(IV)-A Potent Insulin Mimetic Agent, *J. Am. Chem. Soc.*, **1995**, 117(51), 12759-12770.
[27]. K. H. Thompson, B. D. Liboiron, Y. Sun, K. D. D. Bellman, I. A. Setyawati, B. O. Patrick, V. Karunaratne, G. Rawji, J. Wheeler, K. Sutton, S. Bhanot, C. Cassidy, J. H. McNeill, V. G. Yuen, C. Orvig, Preparation and characterization of vanadyl complexes with bidentate maltol-type ligands; in vivo comparisons of anti-diabetic therapeutic potential, *J. Biol. Inorg. Chem.*, **2003**, 8, 66-74.
[28]. T. A. Clark, C. F. Heyliger, M. Kopilas, A. L. Edel, A. Junaid, F. Aguilar, D. D. Smyth, J. A. Thliveris, M. Merchant, H. K. Kim, G. N. Pierce, A tea/vanadate decoction delivered orally over 14 months to diabetic rats induces long-term glycemic stability without organ toxicity, *Metabolism*, **2012**, 61(5), 742–753.
[29]. A. Levina, P. A. Lay, Metal-based anti-diabetic drugs: advances and challenges, *Dalton Trans.*, **2011**, 40, 11675-11686.
[30]. K. H. Thompson, J. Lichter,C. LeBel, M. C. Scaife, J. H. McNeill, C. Orvig, Vanadium treatment of type 2 diabetes: a view to the future, *J. Inorg. Biochem.*, **2009**, 103, 554–558.
[31]. M. Hiromura,Y. Adachi, M. Machida, M. Hattori, H. Sakurai,Glucose lowering activity by oral administration of bis(allixinato)oxidovanadium(IV) complex in streptozotocin-induced diabetic mice and gene expression profiling in their skeletal muscles, *Metallomics*, **2009**, 1, 92–100.
[32]. Y. Adachi, J. Yoshida, Y. Kodera, A. Kahto,J. Takada, H. Sakurai, Bis(allixinato) oxovanadium(IV) Complex Is a Potent Antidiabetic Agent: Studies on Structure−Activity Relationship for a Series of Hydroxypyrone−Vanadium Complexes, *J. Med. Chem.* **2006**, 49, 3251–3256.
[33]. M. Rangel, M. J. Amorim, A. Nunes, A. Leite, E. Pereira, B. de Castro, C. Sousa, Y. Yoshikawa, H. Sakurai, Novel 3-hydroxy-4-pyridinonato oxidovanadium(IV) complexes to investigatestructure/activity relationships, *J. Inorg. Biochem.*, **2009**, 103, 496–502.
[34]. D. Sanna, P. Buglyó, L. Bíró, G. Micera, E. Garribba, Coordinating Properties of Pyrone and Pyridinone Derivatives, Tropolone and Catechol toward the VO^{2+} Ion: An Experimental and Computational Approach, *Eur. J. Inorg. Chem.*, **2012**, 2012(7), 1079–1092.
[35]. Y. Yoshikawa, E. Ueda, K. Kawabe, H. Miyake, T. Takino, H. Sakurai, Y. Kojima, Development of new insulinomimetic zinc(II) picolinate complexes with a $Zn(N_2O_2)$

coordination mode: Structure characterization, in vitro, and in vivo studies, *JBIC Journal of Biological Inorganic Chemistry*, **2002**, 7(1-2), 68–73.
[36]. E. Braunwald, Evaluation of liver function, in Harrison's Principles of Internal Medicine, Ed., **2001,** pp. 1711–1715, *McGraw-Hill, NY, USA.*
[37]. W. Ganong. Review of Medical Physiology, Lange Medical Books, vol. 13 **(2003)**, McGraw-Hill, NY, USA.
[38]. S. Ashakiran, N. Krishnamurthy, S. Navin, S. Patil, Behaviour of serum uric acid and lipid profile in relation to glycemic status in proliferative and non-proliferative diabetic retinopathy, *Current Neurobiology*, **2011**, 2(1), 57–61.
[39]. E. M. Balk, A. Tatsioni, A. H. Lichtenstein, J. Lau, A. G. Pittas, Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials, *Diabetes Care*, **2007**, 30, 2154-2163.
[40]. J. J. Cunningham,A. Z. Fu, P. L. Mearkle, R. G. Brown, Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation, *Metab. Clin. Exp.*, **1994,** 43, 1558-1562.
[41]. W. B. Kinlaw, A. S. Levine, J. E. Morley, S. E. Silvis, C. J. McClain, Abnormal zinc metabolism in type II diabetes mellitus, *Am. J. Med.*,**1983**, 75, 273-277.
[42]. J. Honnorat, M. Accominotti, C. Broussolle, A. C. Fleuret, J. J. Vallon, J. Orgiazzi, Effects of diabetes type and treatment on zinc status in diabetes mellitus, *Biol. Trace. Elem. Res.*, **1992**, 32, 311-316.
[43]. L. Coulson,P. Dandona, Insulin-like Effect of Zinc on Adipocytes,*Diabetes*, **1980**, 29, 665-667.
[44]. A. Shisheva, D. Gefel, Y. Shechter, Insulinlike effects of zinc ion in vitro and in vivo. Preferential effects on desensitized adipocytes and induction of normoglycemia in streptozocin-induced rats, *Diabetes*, **1992**, 41, 982-988.
[45]. M. D. Chen, S. J. Liou, P. Y. Lin, V. C. Yang, P. S. Alexander, W. H. Lin, Effects of zinc supplementation on the plasma glucose level and insulin activity in genetically obese (ob/ob) mice, *Biol. Trace Elem. Res.*, **1998**, 61, 303-311.
[46]. S. F. Simon, C. G. Taylor, Dietary Zinc Supplementation Attenuates Hyperglycemia in db/db Mice, *Exp. Biol. Med.*, **2001**, 226, 43-51.
[47]. H. Sakurai, Y. Yoshikawa, H. Yasui, Current state for the development of metallo pharmaceutics and anti-diabetic metal complexes, *Chem. Soc. Rev.*, **2008**, 37, 2383-2392.
[48]. Y. Kojima, Y. Yoshikawa. *Vitamins*, **2005**, 79, 155-165.
[49]. H. Sakurai, A. Katoh, Y. Yoshikawa, Chemistry and Biochemistry of Insulin-Mimetic Vanadium and Zinc Complexes. Trial for Treatment of Diabetes Mellitus, *Bull.Chem. Soc. Rev.*, **2006**, 79, 1645-1664.
[50]. Y. Yoshikawa, K. Kawabe, M. Tadokoro, Y. Suzuki, N. Yanagihara, A. Nakayama, H. Sakurai, Y. Kojima, New Zinc(II) Complexes with Tetradentate Amino Acid Derivatives: Structure Characterization, Solution Chemistry, and in vitroInsulinomimetic Activity, *Bull. Chem. Soc. Jpn.*, **2002**, 75, 2423-2432.
[51]. Y. Yoshikawa, E. Ueda, H. Miyake, H. Sakurai, Y. Kojima, Insulinomimetic bis(maltolato) zinc(II) Complex: Blood Glucose Normalizing Effect in KK-Ay Mice with Type 2 Diabetes Mellitus, *Biochem. Biophys. Res. Commun.*, **2001**, 281, 1190-1193.
[52]. Y. Adachi, J. Yoshida, Y. Kodera, H. Sakurai, A Highly Potent Insulin–mimetic Zinc(II) Complex with a $Zn(S_2O_2)$ Coordination Mode: Bis(1,6-dimethyl-3-hydroxy-5-methoxy-2-pentyl-1,4-dihydropyridine-4-thionato)zinc(II), *Chem. Lett.*,**2005**, 34, 656- 657.
[53]. Y. Yoshikawa, M. Kondo, H. Sakurai, Y. Kojima, A family of insulinomimetic zinc(II) complexes of amino ligands with Zn(Nn) (n = 3 and 4) coordination modes, *J. Inorg. Biochem.*, **2005**, 99, 1497-1503.
[54]. T. K. Saha, Y. Yoshikawa, H. Sakurai, A [meso-Tetrakis (4-sulfonatophenyl) porphyrinato] zinc(II) Complex As an Oral Therapeutic for the Treatment of Type 2 Diabetic KKAy Mice, *Chem-Med- Chem*, **2007**, 2, 218-225.
[55]. J. Fugono, K. Fujimoto, H. Yasui, K. Kawabe, Y. Yoshikawa, Y. Kojima, H. Sakurai, Metallokinetic Study of Zinc in the Blood of Normal Rats Given Insulinomimetic Zinc(II)

Complexes and Improvement of Diabetes Mellitus in Type 2 Diabetic GK Rats by their Oral Administration, *Drug Metab. Pharmacokinet.,* **2002**, 17, 340- 347.
[56]. Y. Yoshikawa, Y. Adachi, H. Sakurai, A new type of orally active anti-diabetic Zn(II)-dithiocarbamate complex, *Life Sci.,* **2007**, 80, 759-766.
[57]. Y. Adachi, J. Yoshida, Y. Kodera, T. Kiss, T. Jakusch, E. A. Enyedy, Y. Yoshikawa, H. Sakurai, Oral administration of a zinc complex improves type 2 diabetes and metabolic syndromes, *Biochem. Biophys. Res. Commun.,* **2006**, 351, 165-170.
[58]. Y. Yoshikawa, E. Ueda, H. Sakurai, Y. Kojima, Anti-diabetes Effect of Zn(II)/Carnitine Complex by Oral Administration, *Chem. Pharm. Bull.,* **2003**, 51, 230-231.
[59]. M. K. Song, M. J. Rosenthal, S. Hong, D. M. Harris, I. Hwang, I. Yip, M. S. Golub, M. E. Ament, V. L. Go, Synergistic antidiabetic activities of zinc, cyclo (his-pro), and arachidonic acid, *Metabolism*, **2001**, 50, 53-59.
[60]. M. K. Song, I. K. Hwang, M. J. Rosenthal, D. M. Harris, D. T. Yamaguchi, I. Yip, V. L. Go, Anti-Hyperglycemic Activity of Zinc Plus Cyclo (His-Pro) in Genetically Diabetic Goto-Kakizaki and Aged Rats, *Exp. Biol. Med.,* **2003**, 228, 1338-1345.
[61]. H. Fujimura, M. Nozaki, S. Tanaka, T. Akaoka, R. Natsuki, Tranexamic acid/Zn complexes with anti-diabetic effect, *JP Patent*, **2001**, 247458.
[62]. A. Katoh, Y. Matsumura, Y. Yoshikawa, H. Yasui, H. Sakurai, Evaluation of insulin-mimetic activities of vanadyl and zinc(II) complexes from the viewpoint of heterocyclic bidentate ligands, *J. Inorg. Biochem.,* **2009**, 103, 567-574.
[63]. Y. Kojima, H. Sakurai. *JP Patent*, **2001**, 220348.
[64]. S. Karmaker, T. K. Saha, Y. Yoshikawa, H. Sakurai, A Zinc(II)/Poly(γ-glutamic acid) Complex as an Oral Therapeutic for the Treatment of Type-2 Diabetic KKA^{y} Mice,*Macromol. Biosci.,* **2009**, 9, 279-286.
[65]. S. R. Narad, N. N. Mishra, P. Pandey, A. Kumar, Antidiabetic activity of some oral hypoglycemic agents with metal ions on animal model, *Ind. J. Exp. Biol.,* **1996**, 34, 81-82.
[66]. J. Vanco, J. Marek, Z. Trávnícek, E. Racanská, J. Muselík, O. Svajlenová, Synthesis, structural characterization, antiradical and antidiabetic activities of copper(II) and zinc(II) Schiff base complexes derived from salicylaldehyde and beta-alanine, *J. Inorg. Biochem.,* **2008**, 102, 595-605.
[67]. S. K. Jain, P. Patel, K. Rogier, S. K. Jain, Trivalent Chromium Inhibits Protein Glycosylation and Lipid Peroxidation in High Glucose-Treated Erythrocytes, *Antioxid Redox Signal*, **2006**, 8, 238-241.
[68]. K. Schwarz, W. Mertz, Chromium (III) and the glucose tolerance factor, *Arch. Biochem. Biophys.,* **1959**, 85, 292-295.
[69]. J. B. Vincent,Recent advances in the nutritional biochemistry of trivalent chromium, *Proc. Nutr. Soc.,* **2004**, 63, 41-47.
[70]. H. G. Preuss,B. Echard, N. V. Perricone, D. Bagchi, T. Yasmin,S. J. Stohs, Comparing metabolic effects of six different commercial trivalent chromium compounds, *J. Inorg. Biochem.,* **2008**, 102(11), 1986-1990.
[71]. K. Sahin,M. Ondreci, M. Tuzcu, B. Ustundag, G. Cikim, I. H. Ozercan, V. Siramoju, V. Juturu, J. R. Komorowski,Effect of chromium on carbohydrate and lipid metabolism in a rat model of type 2 diabetes mellitus: the fat-fed, streptozotocin-treated rat, *Metabolism,* **2007**, 56(9),1233-1240.
[72]. Y. G. Wang, M. H. Yao, Effects of chromium picolinate on glucose uptake in insulin-resistant 3T3-L1 adipocytes involve activation of p38 MAPK, *J. Nutr. Biochem.,* **2009**, 20(12), 982-991.
[73]. G. W. Evans, D. J. Pouchnik, Composition and biological activity of chromium-pyridine carboxylate complexes, *J. Inorg. Biochem.,* **1993**, 49(3), 177-187.
[74]. R. O. Brown, S. Forloines-Lynn, R. E. Cross, W. D. Heizer, Chromium deficiency after long-term total parenteral nutrition, *Dig. Dis. Sci.,* **1986**, 31(6), 661-664.
[75]. R. A. Anderson, M. M. Polansky, N. A. Bryden, Stability and absorption of chromium and absorption of chromium histidinate complexes by humans, *Biol. Trace Elem. Res.*,**2004**, 101, 211-218.

[76]. F. Dong, M. R. Kandadi, J. Ren, N. Sreejayan, Chromium (D-phenylalanine)$_3$ Supplementation Alters Glucose Disposal, Insulin Signaling, and Glucose Transporter-4 Membrane Translocation in Insulin-Resistant Mice, *J. Nutr.*, **2008**, 138(10), 1846-1851.
[77]. M. Tawkir, S. A. Iqbal, Synthesis, characterization and medical efficacy of Cr(III) complexes ofSulphonyl-ureas, as oral antidiabetics, *Asian J. Pharm. Clin. Res.*, **2012**, 5(4), 129-137.
[78]. P. Mackowiak, Z. Krejpcio,M. Sassek, P. Kaczmarek,I. Hertig, J. Chmielewska, T. Wojciechowicz, D. Szczepankiewicz, D. Wieczorek,H. Szymusiak, K.W. Nowak, Evaluation of insulin binding and signaling activity of newly synthesized chromium(III) complexes in vitro, *Mol. Med. Rep.*, **2010**, 3(2), 347-353.
[79]. D. Stepensky, M. Friedman, W. Srour, I. Raz,A. Hoffman, Preclinical evaluation of pharmacokinetic-pharmacodynamic rationale for oral CR metformin formulation, *J. Control. Release*, **2001**, 71(1), 107-115.
[80]. F. A. Al-Saif,M.S. Refat, Synthesis, spectroscopic, and thermal investigation of transition and non-transition complexes of metformin as potential insulin-mimetic agents,*J. Therm. Anal. Calorim.*, **2013**, 111, 2079-2096.
[81]. S. M. El-Megharbel, Synthesis, Characterization and Antidiabetic Activity of Chromium (III) Metformin Complex, *J. Microb. Biochem. Technol.*, **2015**, 7, 65-75.
[82]. F. Li, Synthesis, Characterization and Preliminary Application of Several Organic Chromium Complexes. *Master's Thesis, Jiangsu University, Zhenjiang, China,* **2009**.
[83]. B. Rosenberg, L. VanCamp, J. E. Trosko, V. H. Mansour, Platinum Compounds: a New Class of Potent Antitumour Agents, *Nature,* **1969**, 222, 385–386.
[84]. J. J. Wilson, S. J. Lippard, Synthetic Methods for the Preparation of Platinum Anticancer Complexes,*Chem. Rev.*, **2014**, 114(8), 4470–4495.
[85]. X. Wang, Z. Guo, Targeting and delivery of platinum-based anticancer drugs, *Chem. Soc. Rev.*, **2013**, 42, 202–224.
[86]. N. J. Wheate, S. Walker, G. E. Craig, R. Oun. The status of platinum anticancer drugs in the clinic and in clinical trials, *Dalton Trans.*, **2010**, 39, 8113–8127.
[87]. N. P. Farrell, Multi-platinum anti-cancer agents: Substitution-inert compounds for tumor selectivity and new targets, *Chem. Soc. Rev.*, **2015**, 44, 8773–8785.
[88]. X. Wang, X. Wang, Z. Guo, Functionalization of Platinum Complexes for Biomedical Applications, *Acc. Chem. Res.*, **2015**, 48(9), 2622–2631.
[89]. G. Jaouen, A. Vessieres, S. Top, Ferrocifen type anti-cancer drugs, *Chem. Soc. Rev.*, **2015**, 44, 8802–8817.
[90]. P. J. O'Dwyer, J. P. Stevenson, S. W. Johnson, Clinical Status of Cisplatin, Carboplatin, and Other Platinum-Based Antitumor Drugs, in: B. Lippert (Ed.), Cisplatin Chemistry and Biochemistry of a Leading Anticancer Drug, *Verlag Helvetica Chimica Acta, Zürich, Switzerland*, **1999**, pp. 1931.
[91]. X. Yao, K. Panichpisal,N. Kurtzman, K. Nugent, Cisplatin nephrotoxicity: a review, *Am. J. Med. Sci.*, **2007**, 334(2), 115–124.
[92]. N. Muhammad, Z. Guo, Metal-based anticancer chemotherapeutic agents, *Curr. Opin. Chem. Biol.*, **2014**, 19, 144-153.
[93]. C. G. Hartinger, P. J. Dyson, Bioorganometallic chemistry--from teaching paradigms to medicinal applications, *Chem. Soc. Rev.*, **2009**, 38(2), 391–401.
[94]. A. Bergamo, G. Sava, Linking the future of anticancer metal-complexesto the therapy of tumour metastases, *Chem. Soc. Rev.*, **2015**, 44, 8818–8835.
[95]. K. D. Mjos,C. Orvig, Metallodrugs in Medicinal Inorganic Chemistry, *Chem. Rev.*, **2014**, 114(8), 4540–4563.
[96]. C. P. Tan,Y. Y. Lu, L.N. Ji, Z.W. Mao, Metallomics insights into the programmed cell death induced by metal-based anticancer compounds, *Metallomics*, **2014**, 6, 978–995.
[97]. N. P. E. Barry, P. J. Sadler, Exploration of the medical periodic table: towards new targets,*Chem. Commun. (Camb.)*, **2013**, 49, 5106–5131.
[98]. G. Jaouen,N. Metzler-Nolte. (Eds.), Medicinal Organometallic Chemistry. Topics in Organometallic Chemistry, *Springer-Verlag*, **2010**.

[99]. G. Gasser,(Ed.), Inorganic Chemical Biology: Principles, Techniques and Applications, *John Wiley & Sons, Ltd, Chichester, UK*, **2014**.
[100]. S. Spreckelmeyer, C. Orvig, A. Casini, Cellular Transport Mechanisms of Cytotoxic Metallodrugs: An Overview beyond Cisplatin, *Molecules*, **2014**, 19(10), 15584–15610.
[101]. E. W. Price, C. Orvig, Matching chelators to radiometals for radiopharmaceuticals, *Chem. Soc. Rev.*, **2014**, 43, 260–290.
[102]. F. Lentz, A. Drescher, A. Lindauer, M. Henke, H. A. Hilger, C. G. Hartinger, M. E. Scheulen, C. Dittrich, B. K. Keppler, U. Jaehde, Pharmacokinetics of a Novel Anticancer Ruthenium Complex (KP1019, FFC14A) in a Phase I Dose-Escalation Study, *Anti-Cancer Drugs*, **2009**, 20(2), 97–103.
[103]. C. G. Hartinger, M. A. Jakupec, S. Zorbas-Seifried, M. Groessl, A. Egger, W. Berger, H. Zorbas, P. J. Dyson, B. K. Keppler, KP1019, a new redox-active anticancer agent--preclinical development and results of a clinical phase I study in tumor patients, *Chem. Biodivers.*, **2008**, 5(10), 2140–2155.
[104]. T. Schilling, K. B. Keppler, M. E. Heim, G. Niebch, H. Dietzfelbinger, J. Rastetter, A. R. Hanauske, Clinical phase I and pharmacokinetic trial of the new titanium complex budotitane, *Invest. New Drugs*, **1996**, 13(4), 327–332.
[105]. K. Strohfeldt,M. Tacke, Bioorganometallic fulvene-derived titanocene anti-cancer drugs,*Chem. Soc. Rev.*, **2008**, 37, 1174–1187.
[106]. I. Ott, R. Gust, Non-Platinum Metal Complexes as Anti-cancer Drugs, *Arch. Pharm. (Weinheim)*, **2007**, 340(3), 117–126.
[107]. M. A. Jakupec, B. K. Keppler, Gallium in Cancer Treatment, *Curr. Top. Med. Chem.*, **2004**, 4(15), 1575–1583.
[108]. M. J. Clarke, Inorganic Chemistry in Biology and Medicine, American Chemical Society, **1980**, Chapter 10, pp. 157–180.
[109]. B. K. Keppler, W. Rupp, Antitumor activity of imidazolium-bisimidazole-tetrachlororuthenate (III). A representative of a new class of inorganic antitumor agents, *J. Cancer Res. Clin. Oncol.*, **1986**, 111(2), 166–168.
[110]. B. K. Keppler, M. Henn, U. M. Juhl, M. R. Berger, R. Niebl, E. E. Wagner, New Ruthenium Complexes for the Treatment of Cancer, *Prog. Clin. Biochem. Med.*, **1989**, 10, 41–69.
[111]. S. Kapitza, M. Pongratz, M. A. Jakupec, P. Heffeter, W. Berger, L. Lackinger, B. K. Keppler, B. Marian, Heterocyclic complexes of ruthenium(III) induce apoptosis in colorectal carcinoma cells, *J. Cancer Res. Clin. Oncol.*, **2005**, 131, 101–110.
[112]. B. K. Keppler, K. G. Lipponer, B. Stenzel, F. Kratzin. Metal Complexes in Cancer Chemotherapy, *Wiley-VCH Verlg GmbH, Weinheim*, **1993**, 187–220.
[113]. C. Riccardi, D. Musumeci, C. Irace, L. Paduano, D. Montesarchio, Ru III Complexes for Anticancer Therapy: The Importance of Being Nucleolipidic, *Eur. J. Org. Chem.*, **2017**, 2017(7), 1100–1119.
[114]. A. Bergamo, C. Gaiddon, J. H. M. Schellens, J. H. Beijnen, G. Sava, Approaching tumour therapy beyond platinum drugs: status of the art and perspectives of ruthenium drug candidates, *J. Inorg. Biochem.*, **2012**, 106, 90–99.
[115]. R. Trondl,P. Heffeter, C. R. Kowol, M. A. Jakupec, W. Berger, B. K. Keppler, NKP-1339, the first ruthenium-based anticancer drug on the edge to clinical application, *Chem. Sci.*,**2014**, 5, 2925-2932.
[116]. E. Alessio, Thirty Years of the Drug Candidate NAMI-A and the Myths in the Field of Ruthenium Anticancer Compounds: A Personal Perspective, *Eur. J. Inorg. Chem.*, **2017**, 2017(12), 1549–1560.
[117]. E. Alessio, G. Balducci, M. Calligaris, G. Costa, W. M. Attia, G. Mestroni, Synthesis, molecular structure, and chemical behavior of hydrogen trans-bis(dimethyl sulfoxide) tetrachlororuthenate (III) and mer-trichlorotris(dimethyl sulfoxide)ruthenium(III): the first fully characterized chloride-dimethyl sulfoxide-ruthenium(III) complexes, *Inorg. Chem.*, **1991**, 30(4), 609–618.

[118]. E. Alessio, G. Mestroni, A. Bergamo, G. Sava, Ruthenium antimetastatic agents, *Curr. Top. Med. Chem.*, **2004**, 4(15), 1525-1535.
[119]. M. Coluccia, G. Sava, G. Salerno, A. Bergamo, S. Pacor, G. Mestroni, E. Alessio, Efficacy of 5-FU Combined to Na[trans-RuCl4(DMSO)Im], A Novel Selective Antimetastatic Agent, on the Survival Time of Mice With P388 Leukemia, P388/DDP subline and MCa Mammary Carcinoma, *Met. Based Drugs*, **1995**, 2(4), 195–199.
[120]. I. Khalaila, A. Bergamo,F. Bussy, G. Sava, P. J. Dyson, The role of cisplatin and NAMI-A plasma-protein interactions in relation to combination therapy, *Int. J. Oncol.*, **2006**, 29(1), 261–268.
[121]. A. Bergamo, T. Riedel, P. J. Dyson, G. Sava, Preclinical combination therapy of the investigational drug NAMI-A(+) with doxorubicin for mammary cancer, *Invest. New Drugs*, **2015**, 33(1), 53–63.
[122]. S. Leijen, S. A. Burgers, P. Baas, D. Pluim, M. Tibben, E. Van Werkhoven, E. Alessio, G. Sava,J.H. Beijnen, J.H.M. Schellens, Phase I/II study with ruthenium compound NAMI-A and gemcitabine in patients with non-small cell lung cancer after first line therapy, *Invest. New Drugs*, **2015**, 33(1), 201–214.
[123]. P. Kaspler, S. Lazic, S. Forward, Y. Arenas,A. Mandel, L. Lilge, A ruthenium(ii) based photosensitizer and transferrin complexes enhance photo-physical properties, cell uptake, and photodynamic therapy safety and efficacy,*Photochem. Photobiol. Sci.*, **2016**, 15, 481–495.
[124]. G. Shi, S. Monro, R. Hennigar, J. Colpitts, J. Fong, K. Kasimova, H. Yin, R. DeCoste, C. Spencer, L. Chamberlain, A. Mandel, L. Lilge, S.A. McFarland, Ru(II) dyads derived from α-oligothiophenes: A new class of potentand versatile photosensitizers for PDT, *Coord. Chem. Rev.*, **2015**, 282–283, 127–138.
[125]. S. Lazic, P. Kaspler, A. Mandel, G. Kulkani, M. Jewett, L. Lilge. Poster: Photodynamic Therapy for Non-Muscle Invasive Bladder Cancer (NMIBC) Mediated by Instilled Photosensitizer TLD1433 and Green Light Activation, *theraLASE Healing at the Speed of Light.*
[126]. M. I. Webb, R. A. Chard, Y. M. Al-Jobory, M. R. Jones, E.W.Y. Wong, C. J. Walsby, Pyridine analogues of the antimetastatic Ru (III) complex NAMI-A targeting non-covalent interactions with albumin, *Inorg. Chem.*, **2012**, 51(2), 954–966.
[127]. G. Mangiapia, G. D'Errico,L. Simeone,C. Irace,A. Radulescu, A. Di Pascale, A. Colonna,D. Montesarchio, L. Paduano,Ruthenium-based complex nanocarriers for cancer therapy, *Biomaterials*, **2012**, 33(14),3770–3782.
[128]. L. Simeone, G. Mangiapia, G. Vitiello, C. Irace, A. Colonna, O. Ortona, D. Montesarchio, L. Paduano, Cholesterol-based nucleolipid-ruthenium complex stabilized by lipid aggregates for antineoplastic therapy, *Bioconjugate Chem.*, **2012**, 23(4), 758–770.
[129]. S. W. Chang, A. R. Lewis, K. E. Prosser, J. R. Thompson, M. Glaskikh, M. B. Bally, J. J. Warren, C. J. Walsby, CF3 Derivatives of the Anticancer Ru(III) Complexes KP1019, NKP-1339, and Their Imidazole and Pyridine Analogues Show Enhanced Lipophilicity, Albumin Interactions, and Cytotoxicity, *Inorg. Chem.*, **2016**, 55(10), 4850–4863.
[130]. C. Mu, S. W. Chang, K. E. Prosser, A. W. Y. Leung, S. Santacruz, T. Jang, J. R. Thompson, D. T. T. Yapp, J. J. Warren, M. B. Bally, T. V. Beischlag, C. J. Walsby, Induction of Cytotoxicity in Pyridine Analogues of the Antimetastatic Ru(III) Complex NAMI-A by Ferrocene Functionalization, *Inorg. Chem.*, **2016**, 55(1), 177–190.
[131]. Z. Adhireksan, G. Palermo, T. Riedel, Z. Ma, R. Muhammad, U. Rothlisberger, P. J. Dyson, C. A. Davey, Allosteric cross-talk in chromatin can mediate drug-drug synergy, *Nat. Commun.*, **2017**, 8, 14860.
[132]. T. Storr. Ligand Design in Medicinal Inorganic Chemistry, John Wiley & Sons Incorporated, **2014**.
[133]. H. Lunk, H. Harti, Discovery, properties and applications of molybdenum and its compounds, *Chem Texts*, 2017, 3(3) **Page number missed**
[134]. S. F. Haddad, B. F. Ali, R. H. Al-Far, J. N. Dawoud, M. I. Alomari, Density functional theory calculations of pentabromidooxomolybdate(V) anion with 2,2′-bipyridinium cation:

Comparison between the calculated geometry and the crystal structure determination at 293 and 90 K, *Polyhedron*, **2010**, 29(3), 1109–1115.
[135]. M. L. H. Nair, D. Thankamani, Synthesis and characterization of oxomolybdenum (V) and dioxomolybdenum (VI) complexes with schiff base derived from isonicotinoylhydrazide, *Indian Journal of Chemistry*, **2009**, 48A, 1212–1218.
[136]. S. K. Patil, V. M. Naik, N. B. Mallur, Synthesis, spectral and antibacterial studies of oxomolybdenum (V) and dioxomolybdenum (VI) complexes with 2-imidazolylmercapto acetohydrazone, *Der Pharma Chemica*, **2012**, 4, 1812–1818.
[137]. K. Saraswati, R. Kant, Synthesis, characterization and biological activity of some molybdenum(VI) complexes, *Der Pharma Chemica*, **2013**, 5, 347–356.
[138]. C. C. L. Pereira, C. V. Diogo, A. Burgeiro, P. J. Oliveira, M. P. M. Marques, S. S. Braga, F. A. A. Paz, M. Pillinger, I. S. Goncalves, DIMEB inclusion of the half-sandwich [CpMo-(CO)2L2]+ complexes (L = NCMe, L2 = 2,2′-biimidazole) and their cytotoxic action against K1735-M2 metastatic cells, *Organometallics*, **2008**, 27(19), 4948–4956.
[139]. E. Mel´endez, Metallocenes as target specific drugs for cancer treatment, *Inorganica Chimica Acta*, **2012**, 393, 36–52.
[140]. U. Ndagi,N. Mhlongo,M. Soliman,Metal complexes in cancer therapy - an update from drug design perspective, *Drug Design, Development and therapy*, **2017**, 11, 599–616.
[141]. P. Martin,M. Marques,L. Coito,A.J. Pombeiro,A.R. Fernandes, Organometallic compounds in cancer therapy: past lessons and future decisions, *Anticancer Agents Med. Chem.,* **2014**, 14(9), 1199-1212.
[142]. J. B. Waem, C. T. Dillon, M. M. Harding, Organometallic anticancer agents: cellular uptake and cytotoxicity studies on thiol derivatives of the anticancer agent, *Medicinal Chemistry*, **2005**, 2093–2099.
[143]. G. R. Willsky, L. H. Chi, M. Godzala, P. J. Kostyniak, J. J. Smee, A. M. Trujillo, J. A. Alfano, W. Ding, Z. Hu, D.C. Crans, Anti-diabetic effects of a series of vanadium dipicolinate complexes in rats with streptozotocin-induced diabetes, *Coord. Chem. Rev.,* **2011**, 225(19-20), 2258–2269.
[144]. J. Nilsson, E. Degerman, M. Haukka, G. C. Lisensky, E. Garribba, Y. Yoshikawa, H. Sakurai, E. A. Enyedy, T. Kiss, H. Esbak, D. Rehder, E. Nordlander, Bis- and tris(pyridyl)amine-oxidovanadium complexes: Characteristics and insulin-mimetic potential, *Dalton Trans.,* **2009**, 38, 7902–7911.
[145]. J. Nilsson, A. A. Shteinman, E. Degerman, E. A. Enyedy, T. Kiss, U. Behrens, D. Rehder, E. Nordlander, Salicylamide and salicylglycine oxidovanadium complexes with insulin-mimetic properties, *J. Inorg. Biochem.,* **2011**, 105(12),1795-1800.