Short thesis for the degree of doctor of philosophy (PhD)

Preparation of half-sandwich type platinum-group metal complexes of *C*- and *N*-glycopyranosyl heterocycles for biological applications

by István Kacsir

Supervisor: Dr. Éva Bokor

UNIVERSITY OF DEBRECEN

Doctoral School of Chemistry

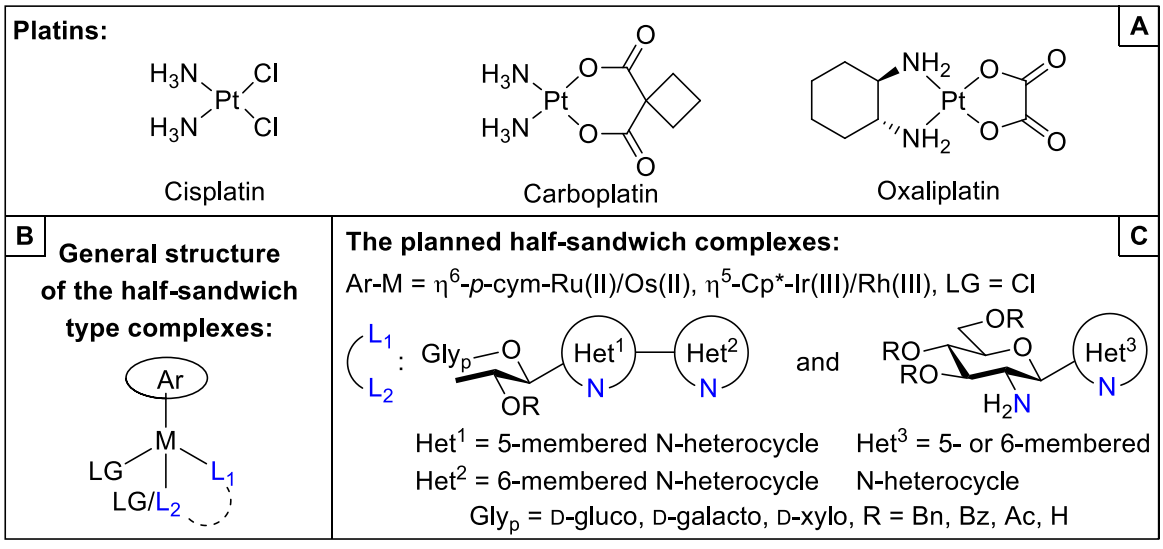
Debrecen, 2024.

1. Introduction and goals of the dissertation

One of the most prominent subclasses of the platinum-group metal complexes is that of the square planar platinum(II) complexes, the platins (Scheme 1, **A**), which are extensively used as chemotherapeutic agents in cancer therapy. Due to the side effects derived from their lack of selectivity and the resistance developed over their prolonged usage, there is an increasing need to find substitutes of platins. For instance, more effective and less harmful drug candidates are searched for among complexes of other platinum-group metal ions.

The study of half-sandwich type complexes represents one direction. The skeleton of these molecules consists of the metal ion and a polyhapto bonded arene or arenyl unit that occupies three coordination sites. The remaining three sites of the coordination sphere are filled by leaving group(s) and mono- or bidentate ligand(s) (Scheme 1, **B**). Among these complexes, derivatives with promising anticancer potency have been found, and several members have also been shown to display other biological activities (e.g. antibacterial, antiviral, antifungal effects).

The aim of my PhD research was to prepare novel half-sandwich platinum-group metal complexes having *C*- and *N*-glycopyranosyl heterocyclic ligands as N,N-chelators (Scheme 1, **C**). The formation of two series of complexes with η^6-*p*-cymene-Ru(II) and -Os(II), and η^5-pentamethylcyclopentadienyl-Ir(III) and -Rh(III) units was envisaged. Cationic complexes containing 5- and 6-membered chelate rings obtained from hetaryl substituted glycopyranosyl azoles and glucosaminyl heterocycles, respectively, were designed as target molecules. The biological effects of these new complexes were planned to be studied in the frame of domestic collaborations.



Scheme 1: The clinically used (**A**), the half-sandwich type (**B**) and the designed metal complexes (**C**)

2. Methods

In the course of my synthetic work, macro-, semimicro- and micro methods of preparative organic chemistry were applied. For monitoring the execution of the reactions thin-layer chromatography analysis (TLC) was performed. The purification of the synthesized compounds was carried out by column chromatography, crystallization or trituration in solvent mixtures. The purity of the isolated compounds was confirmed by their ^{1}H- and ^{13}C-NMR spectra and TLC chromatograms. Their structural elucidation was based on NMR (^{1}H-, ^{13}C-NMR, and in certain cases COSY, HSQC) and mass spectrometric methods (e.g. HR-ESI-MS). The distribution coefficient (logD) of the complexes was determined by UV-Vis spectrophotometry.

* Compound numbering given in the dissertation is applied in the theses.

3. Results

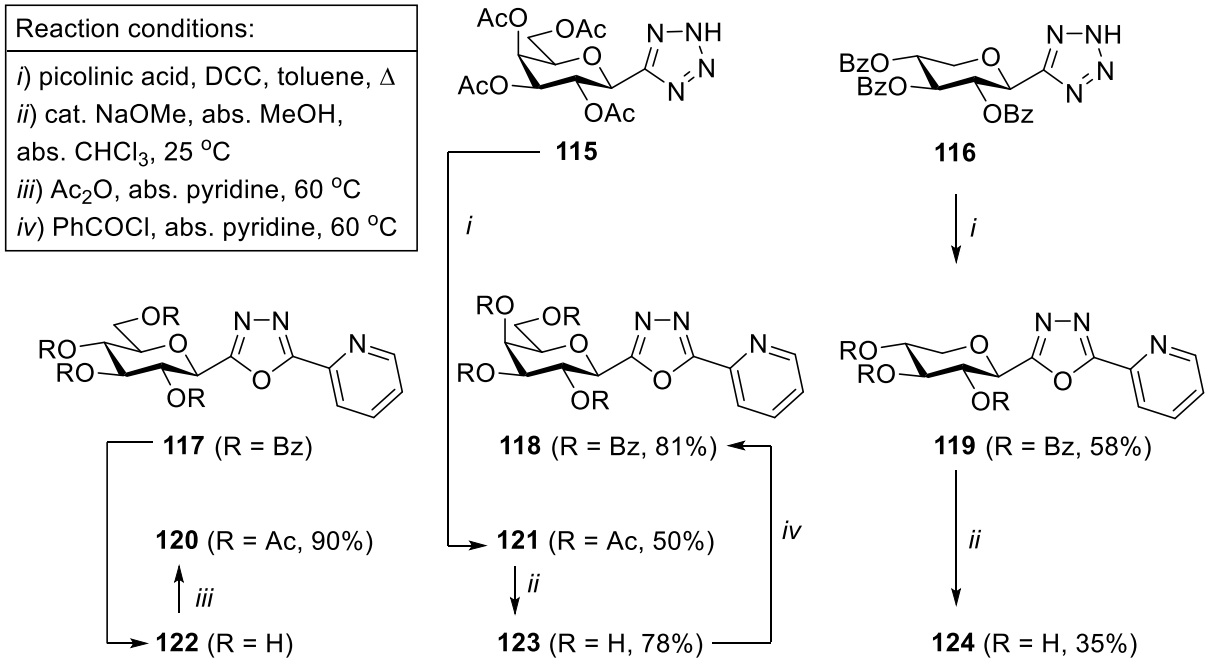
3.1. Synthesis of N,N-chelating heterocyclic monosaccharide ligands

3.1.1. Preparation of hetaryl substituted *C*- and *N*-glycopyranosyl azoles

Hetaryl substituted C*-glycopyranosyl-1,3,4-oxadiazoles and* N*-glucopyranosyl-1,2,3-triazoles were synthesized as ligands of half-sandwich type platinum-group metal complexes containing five-membered chelate ring. These heterocyclic monosaccharides were prepared in* O*-peracylated and* O*-unprotected forms based on 1,3-dipolar cycloadditions and classical* O*-deacylation and* O*-peracylation reactions.*

3.1.1.1. Synthesis of 2-(β-D-glycopyranosyl)-5-(pyridin-2-yl)-1,3,4-oxadiazoles

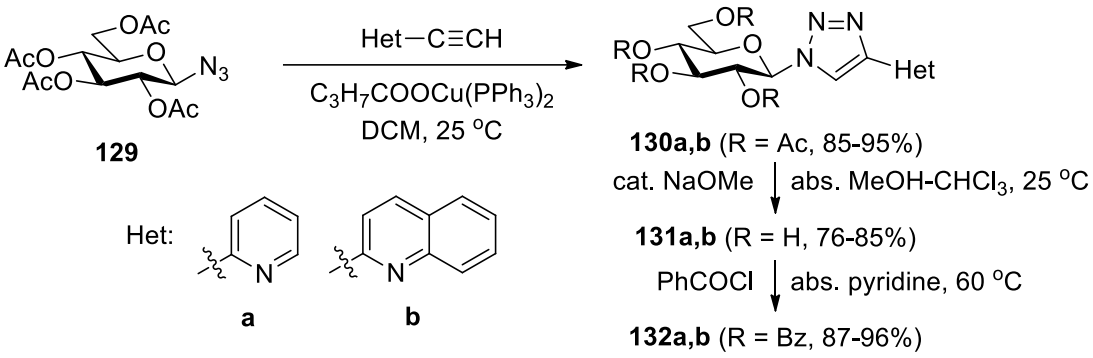
By the adaptation of a ring-transformation method applied earlier in our research group, *O*-peracylated 2-(β-D-galactopyranosyl)- and 2-(β-D-xylopyranosyl)-5-(pyridin-2-yl)-1,3,4-oxadiazoles (**121** (acyl = acetyl), **119** (acyl = benzoyl)) were obtained by the reaction of the corresponding 5-(β-D-glycopyranosyl)tetrazoles **115** and **116** with picolinic acid activated by *N*,*N*-dicyclohexyl carbodiimide (DCC) (Scheme 2). Deacylation of **121** and **119** under Zemplén conditions gave the unprotected **123** and **124**, respectively. Per-*O*-benzoylation of the galactose derivative **123** furnished compound **118**. From resynthesized glucose derivatives **117** and **122** the *O*-peracetylated analog **120** was produced (Scheme 2).



Scheme 2: Preparation of 2-(β-D-glycopyranosyl)-5-(pyridin-2-yl)-1,3,4-oxadiazoles

3.1.1.2. Synthesis of 1-(β-D-glucopyranosyl)-4-hetaryl-1,2,3-triazoles

By azide-alkyne cycloaddition with the use of bis-triphenylphosphano-copper(I)-butyrate catalyst, *O*-peracetylated 1-(β-D-glucopyranosyl)-4-hetaryl-1,2,3-triazoles (**130a,b**) were prepared from glucosyl azide **129** with 2-ethynylpyridine and -quinoline. The *O*-acetyl protecting groups of **130a,b** were then cleaved by the Zemplén method, followed by the treatment of the obtained unprotected derivatives **131a,b** with benzoyl chloride under basic conditions to convert them into the *O*-perbenzoylated analogues **132a,b** (Scheme 3).



Scheme 3: Preparation of 1-(β-D-glucopyranosyl)-4-hetaryl-1,2,3-triazoles

3.1.2. Preparation of heterocyclic glucosamine derivatives

Five- and six-membered C- *and* N-*glucosaminyl heterocycles were synthesized as ligands of half-sandwich type platinum-group metal complexes containing six-membered chelate ring.*

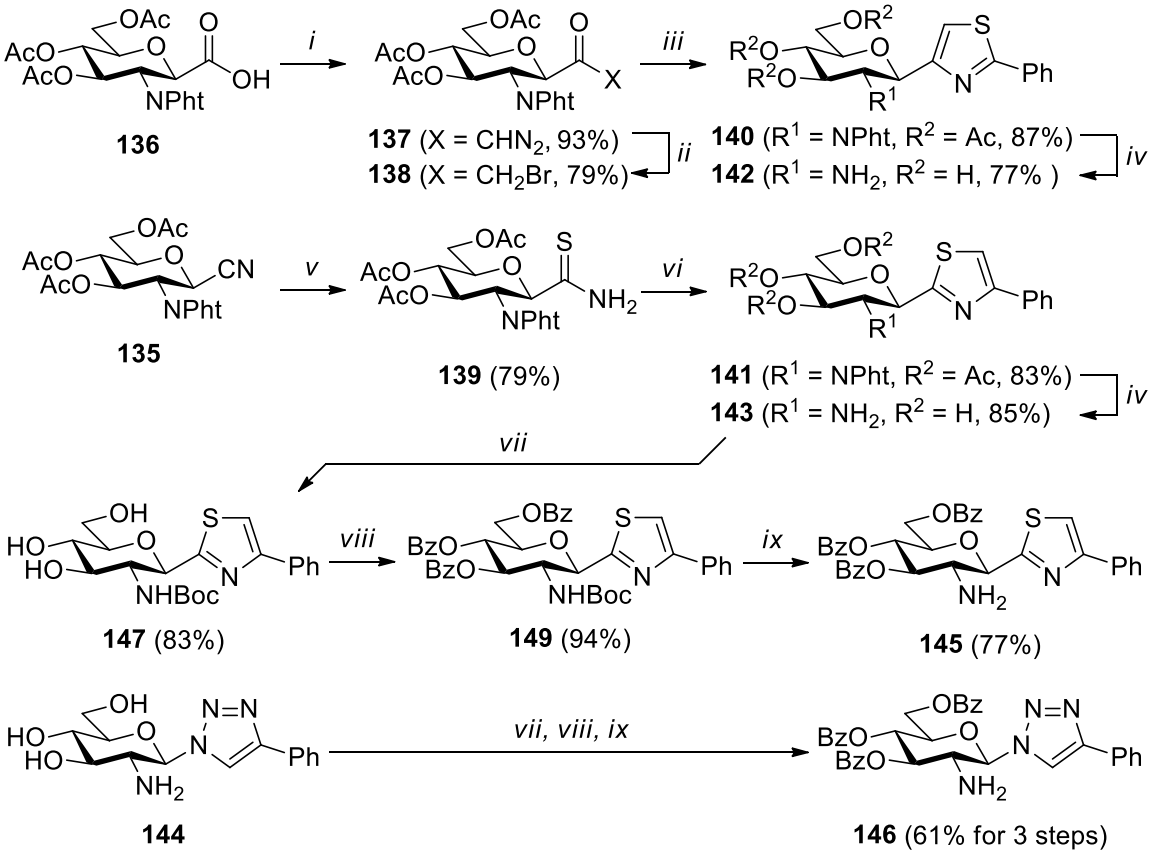
3.1.2.1. Synthesis of C- *and* N-*glucosaminyl azoles*

The preparation of C-*(2'-amino-2'-deoxy-β-D-glucopyranosyl)thiazoles was accomplished by the cyclocondensation reactions of newly synthesized* O-*peracylated* C-*glucosaminyl precursors. By applying a three-step protecting group strategy, an O-perbenzoylated* C-*glucosaminyl thiazole and an* N-*glucosaminyl-1,2,3-triazole were also prepared starting from their unprotected derivatives.*

By the adaptation of literature methods, bromomethyl (2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl) ketone (**138**) and *C*-(2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)thioformamide (**139**) were prepared (Scheme 4). The α-bromoketone **138** was synthesized by the reaction of hydrogen bromide with diazomethyl glycosyl ketone **137** obtained from the 2,6-anhydro aldonic acid derivative **136**. The thioamide **139** was obtained by the treatment of glycosyl cyanide **135** with phosphorus pentasulfide in ethanol.

Isomeric phenyl substituted 4-*C*- and 2-*C*-glucosaminyl thiazoles **140** and **141** were prepared by ring-closure of the α-bromoketone **138** with thiobenzamide and the thioamide **139** with phenacyl bromide, respectively. The glucosaminyl thiazoles **142** and **143** were then synthesized by removal of the *O*-acetyl and phthalimido protecting groups of **140** and **141** with the use of hydrazine hydrate (Scheme 4).

The *O*-perbenzoylated derivative of the 2-*C*-glucosaminyl thiazole **143** (**145** in Scheme 4) was also synthesized in three steps. The *tert*-butoxycarbonylation of the amino group of **143**, followed by the benzoylation of the hydroxyl groups of the resulting **147**, and finally the liberation of the amino group of **149** from the carbamate protection under acidic conditions resulted in the target compound **145** in good overall yield (60% for 3 steps). By applying an analogous reaction sequence, the synthesis of the *O*-perbenzoylated 1-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-4-phenyl-1,2,3-triazole (**146**) was also accomplished starting from compound **144** earlier prepared in our laboratory (Scheme 4).



Conditions: *i*) ClCOOMe, *N*-methylmorpholine, abs. THF, -20 °C, then CH_2N_2 / Et_2O, abs. THF, -20 °C; *ii*) *cc*HBr, THF, 25 °C; *iii*) $PhCSNH_2$, DMF 120 °C; *iv*) $NH_2NH_2 \cdot H_2O$, MeOH, reflux; *v*) P_2S_5, abs. EtOH, reflux; *vi*) $PhCOCH_2Br$, DMF, 100°C; *vii*) Boc_2O, 1,4-dioxane-H_2O (1 : 1), 25 °C; *viii*) PhCOCl, abs. pyridine, 60 °C; *ix*) CF_3COOH, abs. DCM, 25 °C

Scheme 4: Preparation of *C*- and *N*-glucosaminyl azoles

3.1.2.2. Synthesis of C*-glucosaminyl azines*

The preparation of a set of previously unknown C*-glucosaminyl azines was performed based on the nitro-Michael type addition of 3,4,6-tri-*O*-benzyl-2-nitro-*D*-glucal with lithiated heterocycles. These six-membered heterocyclic glucosamine derivatives were synthesized in* O*-perbenzylated,* O*-perbenzoylated and* O*-unprotected forms.*

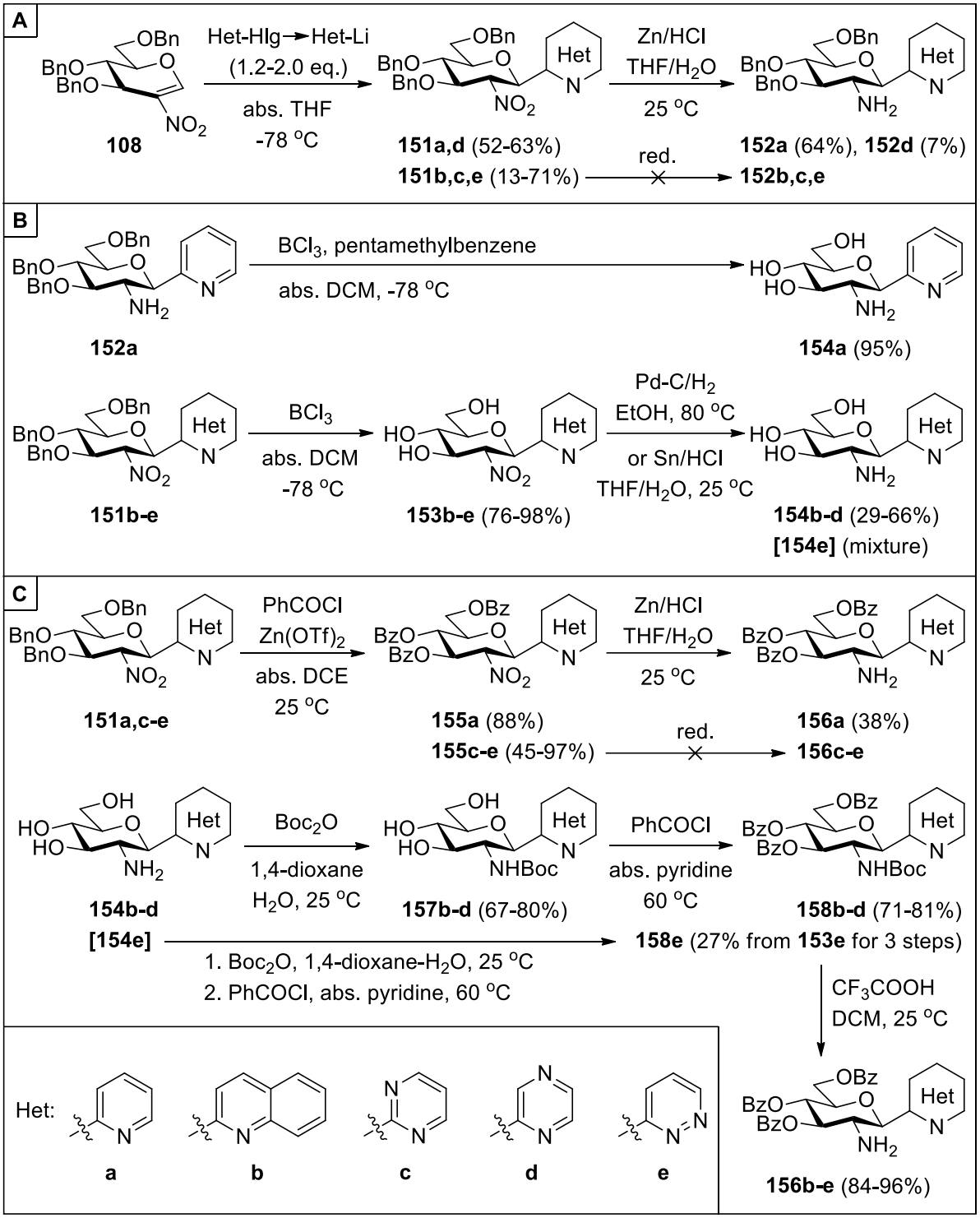
By nitro-Michael type addition of organolithium reagents, obtained from halogenated N-heterocycles with *n*-buthyllithium (Het-Hlg = 2-bromopyridine, 2-bromoquinoline, 2-iodopyrimidine, 2-iodopyrazine, 3-bromopyridazine), to 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal (**108**) *C*-(2'-deoxy-2'-nitro-3',4',6'-tri-*O*-benzyl-β-D-glucopyranosyl)heterocycles **151a-e** were prepared in moderate to good yields (Scheme 5, **A**).

Experiments were carried out for the reduction of the nitro group of these compunds, however, among the planned *O*-perbenzylated glucosamine derivatives **152a-e** only the 2-*C*-glucosaminyl pyridine (**152a**) and pyrazine (**152d**) could be synthesized by using zinc-hydrocloric acid system (Scheme 5, **A**).

The preparation of unprotected *C*-glucosaminyl heterocycles **154a-e** was also studied (Scheme 5, **B**). The pyridine derivative **154a** was obtained by boron trichloride mediated cleavage of the benzyl protecting groups of compound **152a**. The other azine derivatives were produced by debenzylation of the nitro-Michael adducts **151b-e** with boron trichloride, followed by reduction of the nitro group of the resulting **153b-e**. After reductive transformations of **153b-e** into **154b-e** the quinoline (**154b**), pyrimidine (**154c**), and pyrazine (**154d**) derivatives were isolated in pure form and moderate yields, while the pyridazine **154e** could not be separated from the sideproducts.

For the preparation of *O*-perbenzoylated *C*-glucosaminyl heterocycles (**156a-e**) two reaction pathways were investigated (Scheme 5, **C**). First, the exchange of the *O*-benzyl protecting groups of nitro derivatives **151a,c-e** to benzoyl groups was performed by using benzoyl chloride in the presence of $Zn(OTf)_2$, then the conversion of the nitro group of the obtained **155a,c-e** into an amino group was studied under various reductive conditions. Only one of these reactions, the reduction of the pyridine derivative **155a** by zinc-hydrochloric acid was successful, resulting in the glucosamine derivative **156a**. Therefore, the preparation of heterocycles **156b-e** was performed in another way, starting from the unprotected *C*-glucosaminyl azines **154b-e** by applying the three-step protecting group strategy described earlier for the preparation of glucosaminyl azoles. After *tert*-butoxycarbonylation, *O*-perbenzoylation and liberation of the amino group, the expected quinoline, pyrimidine, pyrazine

and pyridazine containing glucosamine derivatives were obtained in good overall yields (**154b-d→157b-d→158b-d→156b-d**, 46-54% for three steps; **153e→[154e]→[157e]→158e→156e**, 26% for four steps).



Scheme 5: Preparation of *C*-glucosaminyl azines

3.2. Synthesis of half-sandwich platinum-group metal complexes with heterocyclic monosaccharides

The above C- *and* N-*glycopyranosyl heterocycles were successfully incorporated as N,N-bidentate ligands into* p-*cymene containing Ru(II) and Os(II), and pentamethylcyclopentadienyl containing Ir(III) and Rh(III) complexes. Thus, sets of novel platinum-group metal complexes with five- and six-membered chelate rings derived from real glycopyranosyl heterocyclic N,N-chelators were achieved.*

3.2.1. Preparation of half-sandwich platinum-group metal complexes containing five-membered chelate ring

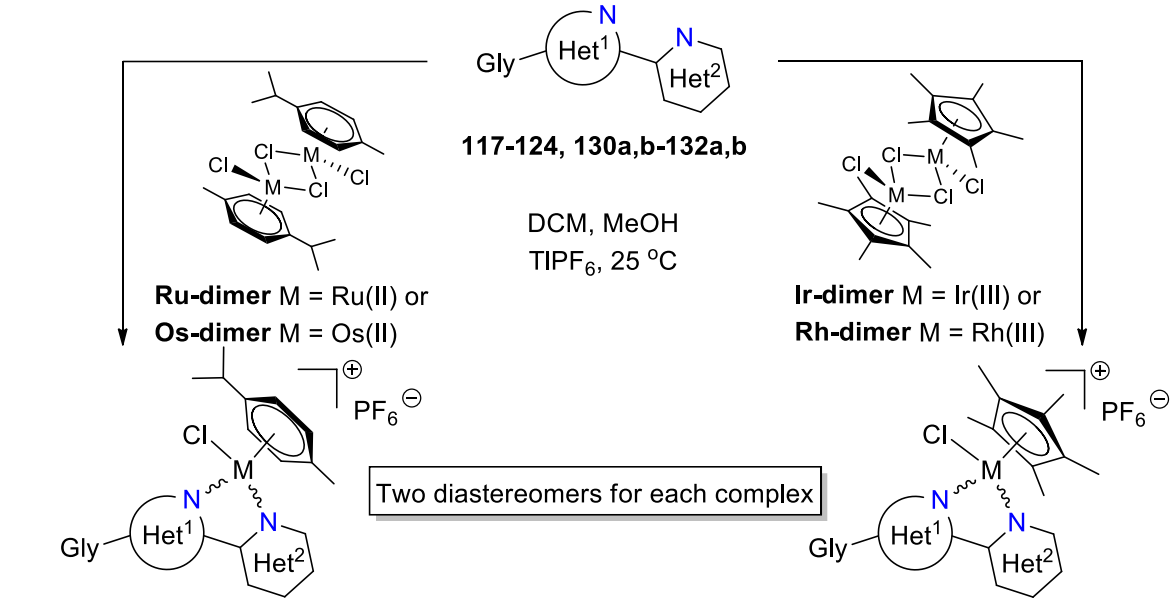
For the preparation of the planned half-sandwich type complexes, the *C*- and *N*-glycopyranosyl azoles (**117-124**, **130a,b-132a,b**) were reacted with dichloro-(η^6-*p*-cymene)-ruthenium(II) and -osmium(II) dimers ([(η^6-*p*-cym)Ru/Os(II)Cl_2]$_2$, **Ru-dimer** and **Os-dimer**) as well as with dichloro-(η^5-pentamethylcyclopentadienyl)-iridium(III) and -rhodium(III) dimers ([(η^5-Cp*)Ir/Rh(III)Cl_2]$_2$, **Ir-dimer** and **Rh-dimer**) in a CH_2Cl_2-MeOH solvent mixure in the presence of the halide abstractor tallium(I)-hexafluorophosphate ($TlPF_6$) (Table 1). The resulting cationic half-sandwich complexes containing five-membered chelate ring (**Ru-117–Ru-124**, **Os/Ir/Rh-117–Os/Ir/Rh-119, Ru-130a,b–Ru-132a,b**, **Os/Ir/Rh-132a,b**) were isolated as mixtures of two diastereomers.

For comparative biological studies, complexes **Ru/Ir-127** and **Ru/Ir-128** were synthesized from previously obtained *O*-perbenzoylated and *O*-unprotected 3-(β-D-glucopyranosyl)-5-(pyridin-2-yl)-1,2,4-oxadiazoles (**127** and **128**) by applying the same reaction conditions described above (Table 1). In addition, 2-phenyl-5-(pyridin-2-yl)-1,3,4-oxadiazole (**126**) and 1-phenyl-4-(pyridin-2-yl)-1,2,3-triazole (**134**) as non-sugar containing azole ligands were used for the preparation of analogous Ru(II) complexes (Table 1, **Ru-126** and **Ru-134**).

One of the isomers of complexes **Ru-127** and **Ir-128** could also be obtained as single crystals. Their structures determined by X-ray diffraction confirmed that, in case of this complex series, the glycopyranosyl azoles as N,N-bidentate ligands formed five-membered chelate rings with the metal ions.

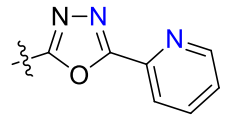
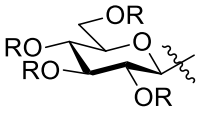
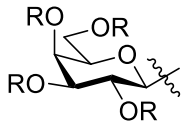
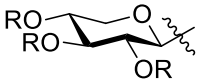
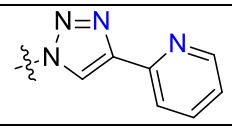
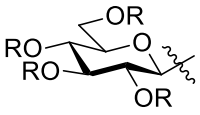
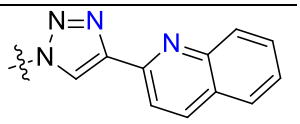
By spectrophotometric measurements the distribution coefficient (logD) of the complexes was also determined in an *n*-octanol-PBS puffer (pH = 7.4). Complexes containing an *O*-perbenzoylated sugar unit with their positive logD values proved to be lipophilic, while complexes with *O*-peracetylated and *O*-unprotected monosaccharides, based on their negative logD values had hydrophilic character (Table 1).

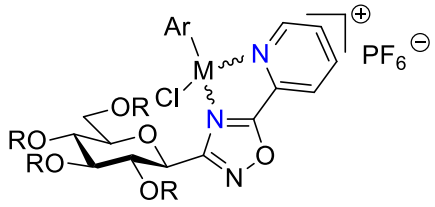
Table 1: Preparation of half-sandwich platinum-group metal complexes of hetaryl substituted azoles



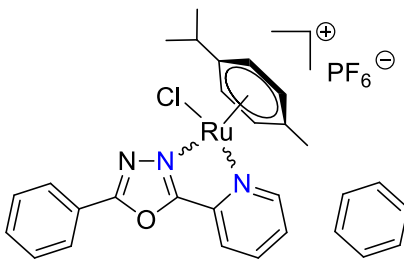
Ru-117–Ru-124, Ru-130a,b–Ru-132a,b
Os-117–Os-119, Os-132a,b

Ir-117–Ir-119, Ir-132a,b
Rh-117–Rh-119, Rh-132a,b

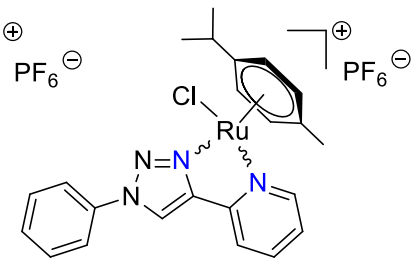
Ligand			Complexation			logD
	Het[1]-Het[2]	Gly	R	Product	Yield (%)	
117			Bz	**Ru/Os/Ir/Rh-117**	71-88	1.46-3.32
120			Ac	**Ru-120**	74	-1.80
122			H	**Ru-122**	87	-1.93
118			Bz	**Ru/Os/Ir/Rh-118**	77-85	1.46-2.87
121			Ac	**Ru-121**	74	-1.29
123			H	**Ru-123**	50	-1.73
119			Bz	**Ru/Os/Ir/Rh-119**	72-87	1.80-2.36
124			H	**Ru-124**	42	-1.73
132a			Bz	**Ru/Os/Ir/Rh-132a**	84-93	1.85-2.85
130a			Ac	**Ru-130a**	98	-1.09
131a			H	**Ru-131a**	90	-1.85
132b			Bz	**Ru/Os/Ir/Rh-132b**	61-80	1.60-2.33
130b			Ac	**Ru-130b**	96	-0.97
131b			H	**Ru-131b**	96	-1.30



Ru-127 (R = Bz, Ar-M = *p*-cim-Ru(II))
Ir-127 (R = Bz, Ar-M = Cp*-Ir(III))
logD = 2.79 (**Ru-127**), 2.87 (**Ir-127**)
Ru-128 (R = H, Ar-M = *p*-cym-Ru(II))
Ir-128 (R = H, Ar-M = Cp*-Ir(III))
logD = -0.96 (**Ru-128**), -1.15 (**Ir-128**)



Ru-126
logD = 1.63



Ru-134
logD = 0.44

3.2.2. Preparation of half-sandwich platinum-group metal complexes containing six-membered chelate ring

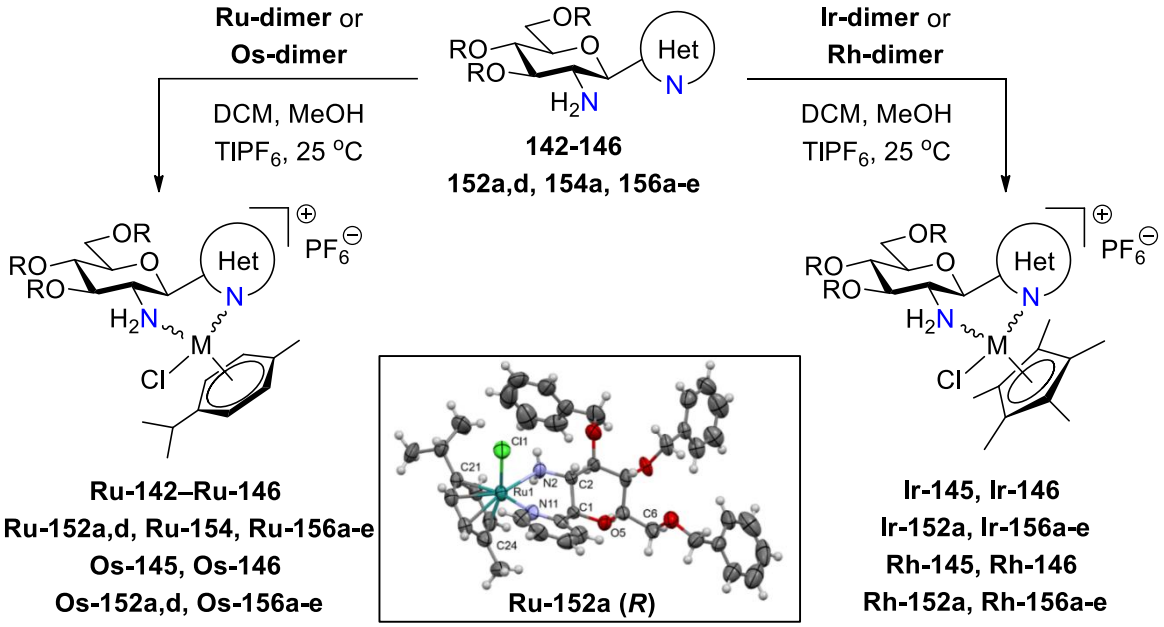
Complexation of the *C*- and *N*-glucosaminyl azoles (**142-146**) and *C*-glucosaminyl azines (**152a,d, 154a, 156a-e**) was performed upon treatment with the chloro-bridged dimers (**Ru/Os/Ir/Rh-dimer**) in the presence of $TlPF_6$ (Table 2). Several complexes of this series were isolated in a single isomeric form (**Ru/Os/Ir/Rh-145**, **Ru/Os/Ir/Rh-152a**, **Ru/Os-152d**, **Ru-154a**, **Ru/Os/Ir/Rh-156a-d**), however, the complexes isolated as mixtures of diastereomers (**Ru-142–Ru-144**, **Ru/Os/Ir/Rh-146**, **Ru/Os/Ir/Rh-156e**) also contained one of the isomers in much higher quantity.

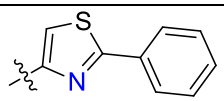
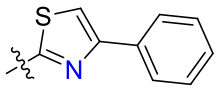
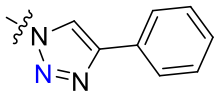
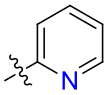
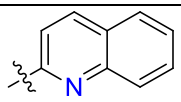
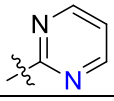
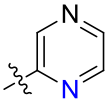
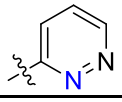
By means of the X-ray structures of single crystals obtained from one of the isomers of **Ru-143** and the stereochemically pure **Ru-152a**, it was confirmed that these heterocyclic glucosamine derivatives, coordinating to the metal ions as N,N-bidentate ligands, formed six-membered chelate rings. Based on the X-ray structure of **Ru-152a**, following the general convention, the absolute configuration of the metal ion was determined as *R*.

In a comparison of the ^{1}H- and ^{13}C-NMR spectra of complexes with *C*-glucosaminyl azines, high similarities of the spectral data of complexes obtained as single isomers and the major component of the complexes isolated as mixtures of diastereoisomers were observed. These results suggest that the absolute configuration of the metal ion in each complex of this set is identical to that of **Ru-152**.

The logD values of these complexes were also determined. With the exception of compound **Ru-154a**, the members of the series proved to be lipophilic (Table 2, $logD > 0$).

Table 2: Preparation of half-sandwich platinum-group metal complexes of five- and six-membered *C*- and *N*-glucosaminyl heterocycles



Ligand		Complexation			logD
	Het	R	Product[#]	Yield (%)	
142		H	**Ru-142**	89	1.51
143		H	**Ru-143**	62	1.34
145		Bz	**Ru/Os/Ir/Rh-145**	82-87	1.32-2.00
144		H	**Ru-144**	66	1.19
146		Bz	**Ru/Os/Ir/Rh-146**	63-93	1.22-2.55
152a		Bn	**Ru/Os/Ir/Rh-152a**	64-93	1.64-3.18
154a		H	**Ru-154a**	43	-1.91
156a		Bz	**Ru/Os/Ir/Rh-156a**	43-86	1.08-2.15
156b		Bz	**Ru/Os/Ir/Rh-156b**	82-96	1.39-2.22
156c		Bz	**Ru/Os/Ir/Rh-156c**	98-99	1.13-1.59
152d		Bn	**Ru/Os-152d**	33-47	2.06-2.64
156d		Bz	**Ru/Os/Ir/Rh-156d**	91-99	1.04-1.42
156e		Bz	**Ru/Os/Ir/Rh-156e**	69-88	1.17-1.41

[#] Isolated as one isomer: **Ru/Os/Ir/Rh-145**, **Ru/Os/Ir/Rh-152a**, **Ru/Os-152d**, **Ru-154a**, **Ru/Os/Ir/Rh-156a-d**
Isolated as a mixture of two diastereomers: **Ru-142–Ru-144**, **Ru/Os/Ir/Rh-146**, **Ru/Os/Ir/Rh-156e**

3.3. Results of the biological studies of the new complexes

The anticancer and antibacterial activities of the prepared complexes were studied in the frame of domestic collaborations. Among these compounds, several derivatives with low micromolar cytostatic and bacteriostatic activity were identified.

The antineoplastic effect of the new complexes was investigated by Dr. Péter Bay's research group at the Department of Medical Chemistry of the University of Debrecen. Several complexes showed cytostatic activity against various cancer cells (e.g. carcinoma, sarcoma, lymphoma), while their uncomplexed ligands as well as the chloro-bridged dimeric precursors proved to be inactive. These studies also revealed that the active complexes induced oxidative stress *via* reactive oxygen species production.

Among structure-activity relationships obtained from the comparison of the biological effects of the complexes with five-membered chelate ring (Scheme 6, **A**), the followings are highlighted:

- Complexes of the heterocyclic sugar derivatives benzoylated on their hydroxyl groups displayed cytostatic activity. With these bulky, hydrophobic protecting groups, the cationic complexes became lipophilic (logD > 0, for the most active complexes logD ≥ 2), and based on these results, this characteristic was necessary for the biological effectiveness.
- The configuration of the sugar unit of the N,N-bidentate ligands had no significant effect on the biological activity, while the azole ring greatly influenced it.
- The Ru(II) and Os(II) complexes with a neutral *p*-cymene ligand exerted better anticancer activities than the Ir(III) and Rh(III) analogs containing a negatively charged pentamethylcyclopentadienyl (Cp*) moiety.
- The potency of the complexes with *O*-perbenzoylated glycosyl azoles was 1-2 orders of magnitude higher than that of their counterparts containing non-sugar based phenylazoles.

Certain selectivity was also observed in the effect of the members of this series by showing inactivity on the healty, non-transformed primary human skin fibroblasts.

The *p*-cymene containg Os(II) complex of the *O*-perbenzoylated 1-(β-D-glucopyranosyl)-4-(quinolin-2-yl)-1,2,3-triazole (**Os-132b**) was found to be the most effective compound of the set displaying submicromolar cytostatic activity on A2780 ovarian cancer cells (Scheme 6, **A**). The effect of this complex was superior to the clinically used cisplatin, and it was also potent at submicromolar concentration on the cisplatin resistant A2780R cancer cell line.

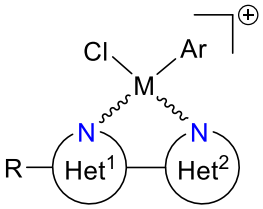
In the series of the complexes with six-membered chelate ring, the complexes having glucosaminyl azoles had no anticancer potency, while some members of the complexes with

O-perbenzylated and -perbenzoylated *C*-glucosaminyl azines exerted micromolar cytostatic activity. Among them, the pyridine containing **Ru-152a** highlighted in Scheme 6 **B** was the most effective, showed, however, no selectivity.

The antibacterial activity of the complexes was studied by Dr. Gábor Kardos's research group at the Department of Metagenomics of the University of Debrecen. Most of the complexes having antineoplastic activity (e.g. **Os-132b** and **Ru-152b** shown in Scheme 6) exerted also bacteriostatic effect against multiresistant Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*).

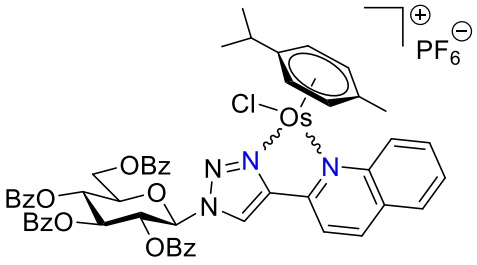
A

Structure-activity relationships of the complexes containing five-membered chelate ring:



If R = $R'_{3/4}$-Gly_p
R' = Bz >>> Ac, H (inactive)
Gly_p = β-D-gluco ~ β-D-galacto > β-D-xylo
R = $Bz_{3/4}$-Gly_p >> Ph
Het^1 = 1,2,3-triazole > 1,3,4-oxadiazole >>> 1,2,4-oxadiazole (inactive)
Het^2 = quinolin-2-yl > pyridin-2-yl
Ar-M = η^6-*p*-cym-Ru(II)/Os(II) > η^5-Cp*-Ir(III) >> η^5-Cp*-Rh(III)

The most efficient complex of the set:



Os-132b

Cytostatic activity:

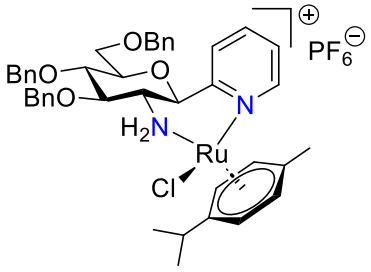
Cell line	IC_{50} [μM]
A2780	0.58
A2780R	0.43
ID8	0.36
Capan2	1.35
Saos	1.29
Fibroblast	inactive

Cisplatin: IC_{50} = 1.21 μM (A2780)

Bacteriostatic activity (MIC):
5-40 μM (*Staphylococcus aureus*)
10 μM (*Enterococcus faecalis*)

B

The most potent derivative of the complexes containing six-membered chelate ring:



Ru-152a

Cytostatic activity:

Cell line	IC_{50} [μM]
A2780	1.86
ID8	2.54
Capan2	2.25
MCF7	2.30
U251	3.97
Fibroblast	9.62

Bacteriostatic activity (MIC):
5 μM (*Staphylococcus aureus*)
5-10 μM (*Enterococcus faecalis*)

A2780: ovarian carcinoma; A2780R: cisplatin resistant ovarian carcinoma; Capan2: pancreatic adenocarcinoma; Saos: osteosarcoma; ID8: ovarian cancer; MCF7: breast cancer; U251: glioblastoma; Fibroblast: healty, non-transformed human primary skin fibroblasts

Scheme 6: The structure-activity relationships of the prepared complexes and biological results of the most active derivatives

4. Possible applications of the results

In the course of my PhD study, the synthesis of novel half-sandwich platinum-group metal complexes with 5- and 6-membered *C*- and *N*-glycopyranosyl heterocycles as N,N-bidentate ligands was accomplished.

The biological study of the prepared complexes revealed several derivatives with (sub)micromolar cytostatic activity, whose effect was comparable to or better than that of the clinically used chemotherapeutic agents, platins. In addition, these molecules showed efficacy against cisplatin resistant ovarian cancer cells. Based on these promising results, these compounds may have the potential to become substitutes of the platins after further biological studies.

The complexes with anticancer potency also displayed bacteriostatic activity against multiresistant Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*). Thus, these molecules may also serve as leads in the development of drug candidates suitable for combatting bacterial infections against which no effective agent is currently available.

By means of the biological results of the large number of synthesized complexes structure-activity relationships were also revealed, which may be good starting points in the future for the design and discovery of new, even more efficient complexes with anticancer and/or antibacterial potencies.

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/233/2024.PL
Subject: PhD Publication List

Candidate: István Kacsir
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10093384

List of publications related to the dissertation

Foreign language scientific articles in international journals (5)

1. **Kacsir, I.**, Sipos, A., Kiss, T., Major, E., Bajusz, N., Tóth, E., Buglyó, P., Somsák, L., Kardos, G., Bai, P., Bokor, É.: Half sandwich-type osmium, ruthenium, iridium and rhodium complexes with bidentate glycosyl heterocyclic ligands induce cytostasis in platinum-resistant ovarian cancer cells and bacteriostasis in Gram-positive multiresistant bacteria.
   Front. Chem. 11, 1-18, 2023. EISSN: 2296-2646.
   DOI: http://dx.doi.org/10.3389/fchem.2023.1086267
   IF: 5.5 (2022)

2. **Kacsir, I.**, Sipos, A., Major, E., Bajusz, N., Bényei, A., Buglyó, P., Somsák, L., Kardos, G., Bai, P., Bokor, É.: Half-sandwich type platinum-group metal complexes of C-Glucosaminyl azines: syntheses, antineoplastic and antimicrobial activities.
   Molecules. 28 (7), 1-55, 2023. ISSN: 1420-3049.
   DOI: http://dx.doi.org/10.3390/molecules28073058
   IF: 4.6 (2022)

3. **Kacsir, I.**, Sipos, A., Bényei, A., Janka, E. A., Buglyó, P., Somsák, L., Bai, P., Bokor, É.: Reactive Oxygen Species Production Is Responsible for Antineoplastic Activity of Osmium, Ruthenium, Iridium and Rhodium Half-Sandwich Type Complexes with Bidentate Glycosyl Heterocyclic Ligands in Various Cancer Cell Models.
   Int. J. Mol. Sci. 23 (2), 1-39, 2022. ISSN: 1661-6596.
   DOI: http://dx.doi.org/10.3390/ijms23020813
   IF: 5.6

4. Balázs, B., Tóth, Z., **Kacsir, I.**, Sipos, A., Buglyó, P., Somsák, L., Bokor, É., Kardos, G., Bai, P.: Targeting multiresistant Gram-positive bacteria by ruthenium, osmium, iridium and rhodium half-sandwich type complexes with bidentate monosaccharide ligands.
   Front. Chem. 10, 1-9, 2022. EISSN: 2296-2646.
   DOI: http://dx.doi.org/10.3389/fchem.2022.868234
   IF: 5.5

5. **Kacsir, I.**, Sipos, A., Ujlaki, G., Buglyó, P., Somsák, L., Bai, P., Bokor, É.: Ruthenium half-sandwich type complexes with bidentate monosaccharide ligands show antineoplastic activity in ovarian cancer cell models through reactive oxygen species production.
Int. J. Mol. Sci. 221, 1-41, 2021. ISSN: 1661-6596.
DOI: http://dx.doi.org/10.3390/ijms221910454
IF: 6.208

List of other publications

Foreign language scientific articles in international journals (3)

6. Nagy, S., Tóth, E., **Kacsir, I.**, Makai, A., Bényei, A., Buglyó, P.: Effect of the replacement of tripodal 4N donors by two 2N chelators on the redox and cytotoxic activity of maltolato and deferipronato containing Co(III) complexes.
J. Inorg. Biochem. 220, 1-10, 2021. ISSN: 0162-0134.
DOI: http://dx.doi.org/10.1016/j.jinorgbio.2021.111372
IF: 4.336

7. Sanna, D., Ugone, V., Buglyó, P., Nagy, S., **Kacsir, I.**, Garribba, E.: Speciation in aqueous solution and interaction with low and high molecular mass blood bioligands of $[V^{IV}O(oda)(H_2O)_2]$, a V compound with in vitro anticancer activity.
Inorg. Chim. Acta. 472, 127-138, 2018. ISSN: 0020-1693.
DOI: http://dx.doi.org/10.1016/j.ica.2017.07.064
IF: 2.433

8. Buglyó, P., **Kacsir, I.**, Kozsup, M., Nagy, I., Nagy, S., Bényei, A., Kováts, É., Farkas, E.: Tuning the redox potentials of ternary cobalt(III) complexes containing various hydroxamates.
Inorg. Chim. Acta. 472, 234-242, 2018. ISSN: 0020-1693.
DOI: http://dx.doi.org/10.1016/j.ica.2017.07.026
IF: 2.433

DEBRECENI EGYETEM Egyetemi és Nemzeti Könyvtár

Total IF of journals (all publications): 36,61
Total IF of journals (publications related to the dissertation): 27,408

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

09 May, 2024

Conference participations

Oral presentation

1. E. Szennyes, S. Kun, É. Bokor, **I. Kacsir**, D. T. Barr, J. M. Hayes, L. Somsák:
   New C- *and* N-*glucopyranosyl azoles as potential inhibitors of glycogen phosphorylase*
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése, Mátrafüred, 2018. május 23-25.
2. **I. Kacsir**, É. Bokor, P. Buglyó, A. Bényei, T. Docsa, Á. Sipos, L. Somsák:
   Preparation of new C- *and* N-*glycopyranosyl azoles and their use as bidentate ligands for the formation of half-sandwich Ru(II) complexes*
   International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics, Mátrafüred, 2019. május 22-24.
3. **Kacsir I.**, Bokor É., Kiss M., Somsák L., Buglyó P., Sipos A., Ujlaki Gy. Bay. P.:
   Heterociklusos monoszacharidok félszendvics platinafém komplexeinek előállítása és antineoplasztikus aktivitása
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság online szakmai előadónap, 2021. június 14.
4. **I. Kacsir**, É. Bokor, P. Buglyó, A. Bényei, T. Docsa, Á. Sipos, L. Somsák:
   Preparation of half-sandwich type platinum-group metal complexes with glucosaminyl heterocyclic ligands
   15th Bratislava Symposium on Saccharides, Smolenice Castle, Slovakia, 20-24 June, 2022. FP10, Book of Abstracts p. 76.
5. **I. Kacsir**, A. Sipos, P. Buglyó, P. Bai, L. Somsák, É. Bokor:
   Preparation of heterocyclic glucosamine derivatives and their half-sandwich platinum-group metal complexes
   Debrecen Colloquium on Carbohydrates 2020 in 2022, Rezső Bognár Memorial Conference on Glycomimetics, Debrecen, Hungary, 24-27 August, 2022. OL13, Book of Abstracts p. 50.

Poster presentations

6. **Kacsir I.**, Bokor É., Buglyó P., Somsák L.:
   C-*Glikozil N-heterociklusok és Ru(II) komplexeik előállítása*
   I. Fiatal Kémikusok Fóruma Szimpózium, Debrecen, 2019. április 3-5.
7. **Kacsir I.**, Bokor É., Buglyó P., Bényei A., Docsa T., Sipos Á., Somsák L.:
   C- *és* N-*Glikopiranozil azolok, valamint félszendvics típusú Ru(II) komplexeik előállítása*
   MKE Vegyészkonferencia 2019, Eger, 2019. június 24-26. P54.
8. L. Somsák, **I. Kacsir**, É. Bokor, P. Buglyó, A. Bényei, T. Docsa, Á. Sipos:
   Synthesis of new C- *and* N-*glycopyranosyl azoles and their half-sandwich Ru(II) complexes*
   XXth European Carbohydrate Symphosium (EUROCARB 2019), Leiden, Netherlands, 30 June – 4 July, 2019. P214, Poster Abstracts p. 228.
9. **Kacsir I.**, Sipos A., Buglyó P., Bai P., Somsák L., Bokor É.
   Glükózaminil heterociklusok és félszendvics platinafém komplexeik előállítása
   MKE Vegyészkonferencia, Eger, 2022. június 15-17. P17, p. 89.

Patent

1. P. Bay; É. Bokor, L. Somsák, I. Kacsir, P. Buglyó, A. Sipos, G. Kardos, Z. Tóth, Gy. A. Kiss: *Half-sandwich transition metal complexes and uses thereof.* Nemzetközi szabadalom, 2023, WO2023041947.