The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Synthesis, structure and biological activity of novel 4,5-dihydro-1*H*-imidazol-2-yl-phthalazine derivatives and their copper(II) complexes

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

Łukasz Balewski [1,*], Jakub Kokoszka [1], Joanna Fedorowicz [1], Ilina Polina [2], Tammela Päivi [2], Maria Gdaniec [3], and Anita Kornicka [1]

[1] Department of Chemical Technology of Drugs, Medical University of Gdańsk
[2] Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki
[3] Faculty of Chemistry, A. Mickiewicz University, Poznań

* Corresponding author: lukasz.balewski@gumed.edu.pl

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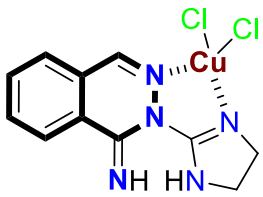

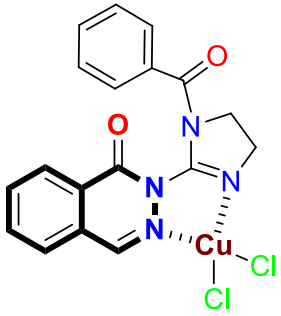

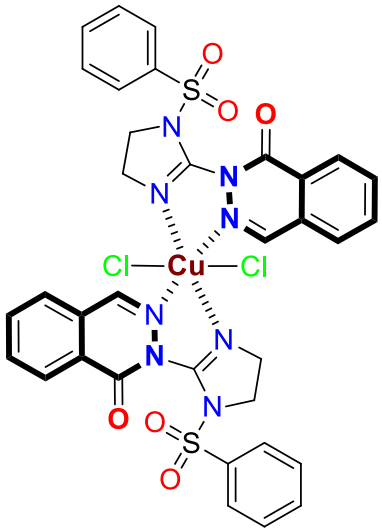

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Abstract:

As a continuation of our previous investigations aimed at the synthesis of novel nitrogen-containing heterocycles and their complexes with antiproliferative activity, we have now prepared two series of compounds incorporating a phthalazine ring at the position C_2 of 4,5-dihydro-1*H*-imidazole: *N*-[2-(1-aroyl-4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-ylidene]benzamides and *N*-{2-[1-(arylsulfonyl)-4,5-dihydro-1*H*-imidazol-2-yl]phthalazin-1(2*H*)-ylidene}benzenesulfonamides.

Benzamides and benzenesulfonamides can be transformed into corresponding 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-one derivatives. Such ligands are susceptible to the reaction with copper(II) chloride giving rise to the formation of corresponding copper(II) complexes.

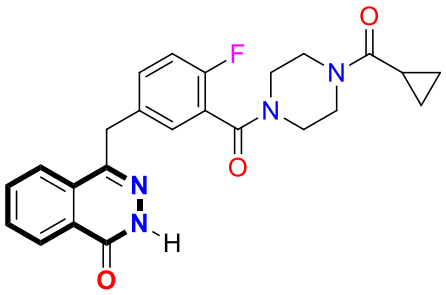
Structures of the ligands and copper(II) complex were confirmed by IR, NMR spectroscopic data, elemental analysis, as well as single crystal X-ray analysis.

The most promising results of biological studies were obtained for copper(II) complex with 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine towards the cervical cancer cell line HeLa (IC_{50} = 2.13 μM) without a toxic effect against normal non-tumorigenic mouse fibroblasts BALB/3T3 (IC_{50} = 135.30 μM), which pointed towards its selectivity as a potential antitumor agent.

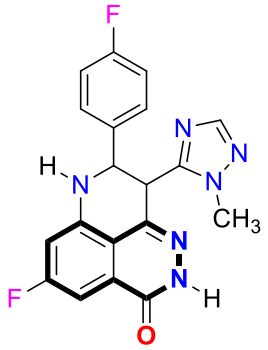
Keywords: **copper complexes, cytotoxicity, imidazolines, phthalazines, X-ray**

Introduction

Compounds with a central phthalazine skeleton have been studied for potential therapeutic applications due to their pronounced anticancer activity [1-5]. Worth noting is the fact that phthalazin-1(2*H*)-one moiety is present in the structure of poly(ADP-ribose) polymerase inhibitors *Olaparib* used for the treatment of ovarian, breast, and prostate cancers [6] and *Talazoparib* developed by *Pfizer* for the treatment of advanced breast cancer with germline BRCA mutations.



Olaparib

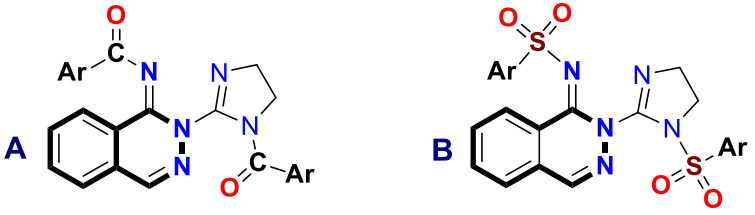


Talazoparib

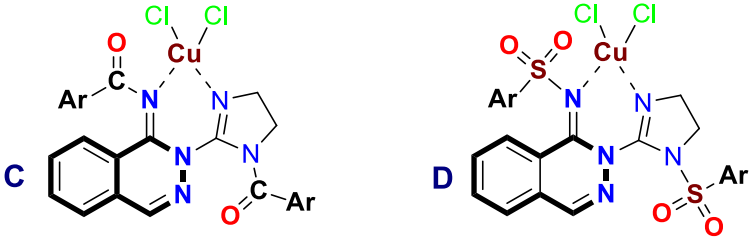
On the other hand, considerable research has been devoted to copper(II) complexes which display strong antiproliferative properties. Their antitumor effect results from various mechanisms [7-10]. Noteworthy is the fact, that metal complexes possess enhanced biological activity and selectivity toward cancer cells compared with the free ligands.

Introduction

As a continuation of our previous investigations aimed at the synthesis of novel *nitrogen-containing heterocycles* and their *copper(II) complexes* [11,12] with potential biological activities, we have now prepared two series of compounds incorporating phthalazine ring at the position C_2 of 4,5-dihydro-1*H*-imidazole: *N*-[2-(1-aroyl-4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-ylidene)benzamides (**A**) and *N*-{2-[1-(arylsulfonyl)-4,5-dihydro-1*H*-imidazol-2-yl]phthalazin-1(2*H*)-ylidene}benzene-sulfonamides (**B**).

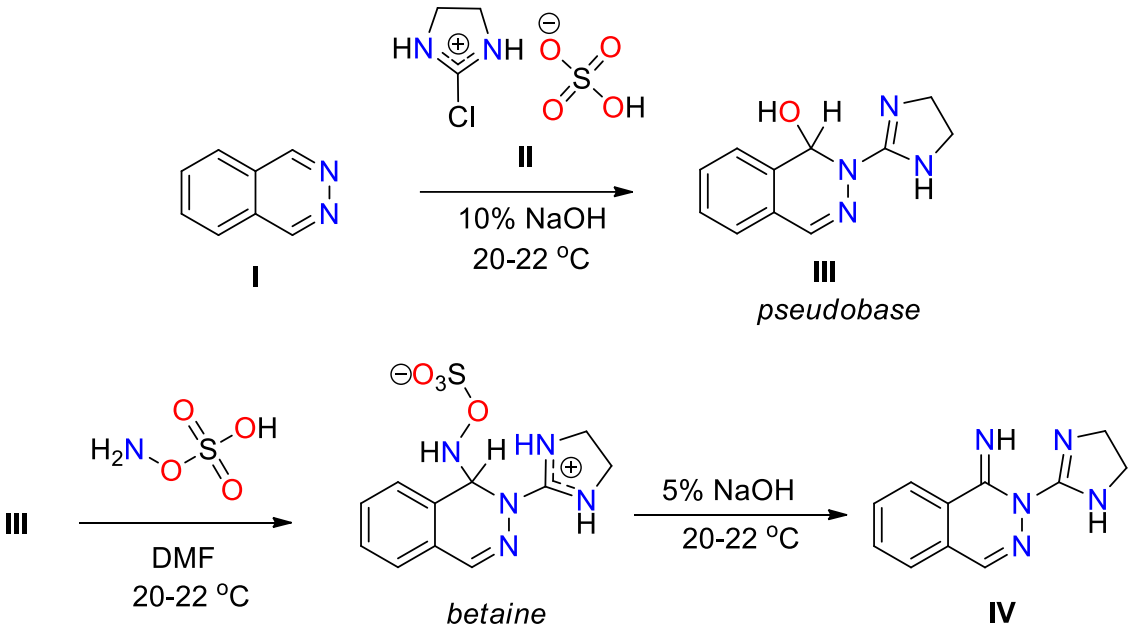


Benzamides **A** or benzenesulfonamides **B** may be susceptible to the reaction with $CuCl_2$ giving rise to the formation of corresponding copper(II) complexes **C** and **D**. According to literature data [13], the designed compounds may exhibit both antitumor or/and superoxide dismutase-mimicking properties.



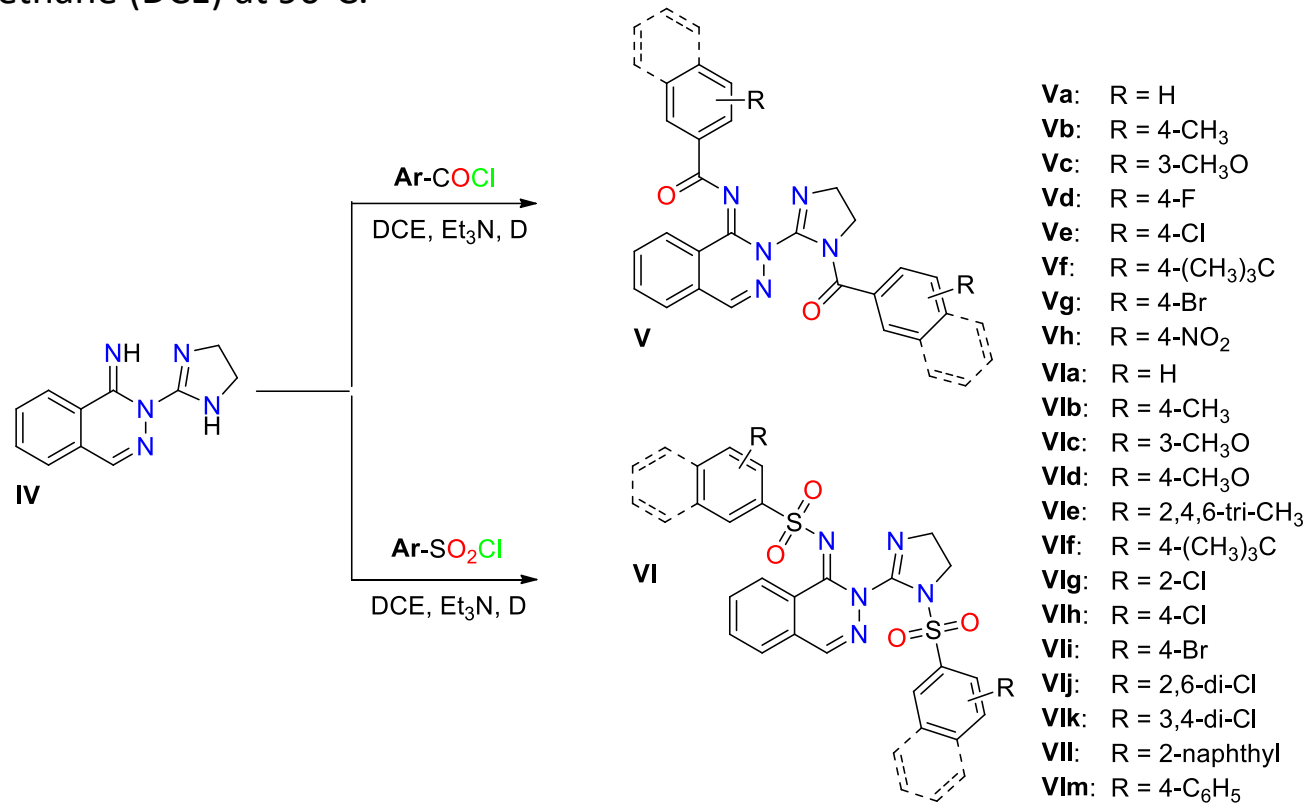
Results and discussion

The starting phthalazine (**I**) in the reaction with 2-chloro-4,5-dihydro-1*H*-imidazole (**II**) gives rise to the formation of *pseudobase*: 2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazin-1-ol (**III**). Then, compound **III** upon treatment with (aminooxy)sulfonic acid (HOSA) in anhydrous DMF yields *betaine* which under basic condition gives the desired 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IV**).



Results and discussion

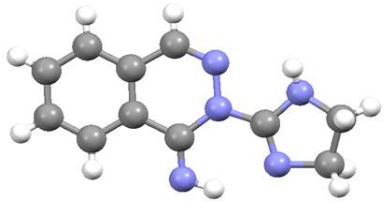
Our synthetic interest focused on the reactions of 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IV**) with acyl and sulfonyl halides. Upon treatment of compound **IV** with a variety of acyl and sulfonyl chlorides corresponding di-substituted: benzamides **V** and sulfonamides **VI** were formed in good yields. The reactions were carried out in anhydrous dichloroethane (DCE) at 90°C.

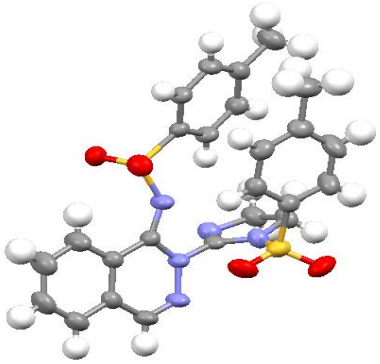


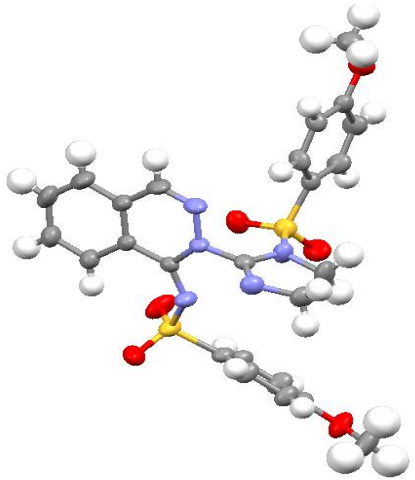
Va: R = H
Vb: R = 4-CH_3
Vc: R = 3-CH_3O
Vd: R = 4-F
Ve: R = 4-Cl
Vf: R = 4-$(CH_3)_3C$
Vg: R = 4-Br
Vh: R = 4-NO_2
VIa: R = H
VIb: R = 4-CH_3
VIc: R = 3-CH_3O
VId: R = 4-CH_3O
VIe: R = 2,4,6-tri-CH_3
VIf: R = 4-$(CH_3)_3C$
VIg: R = 2-Cl
VIh: R = 4-Cl
VIi: R = 4-Br
VIj: R = 2,6-di-Cl
VIk: R = 3,4-di-Cl
VIl: R = 2-naphthyl
VIm: R = 4-C_6H_5

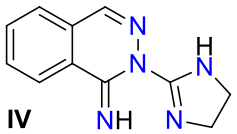
Results and discussion

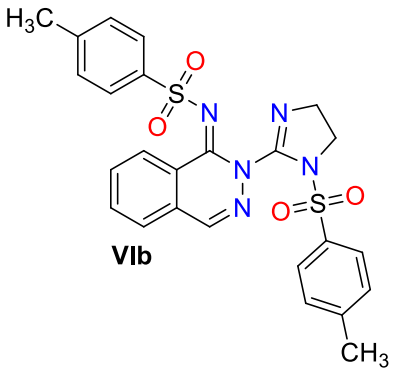
Crystallographic structures of compounds: IV, VIb and VId

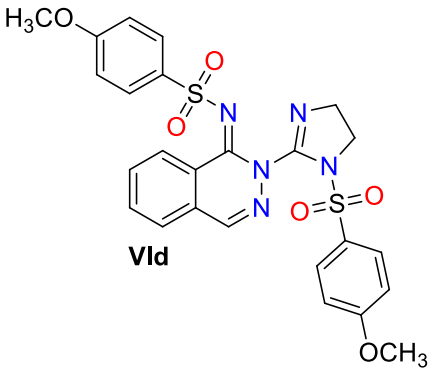






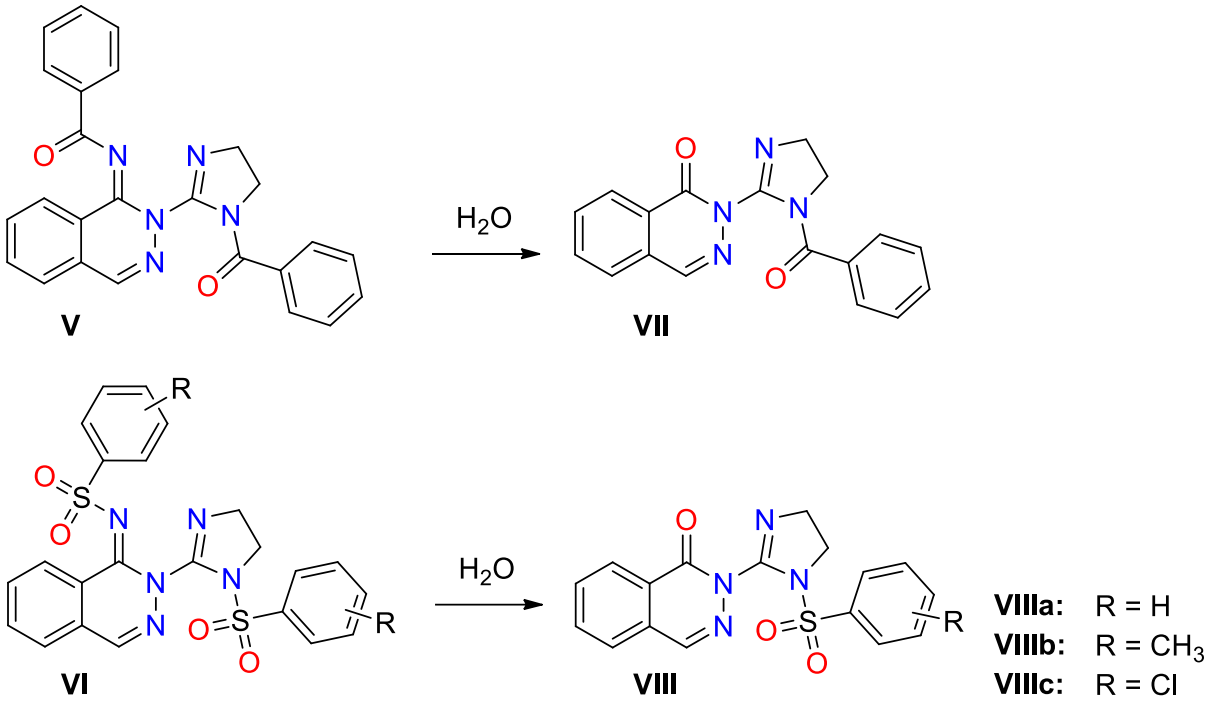






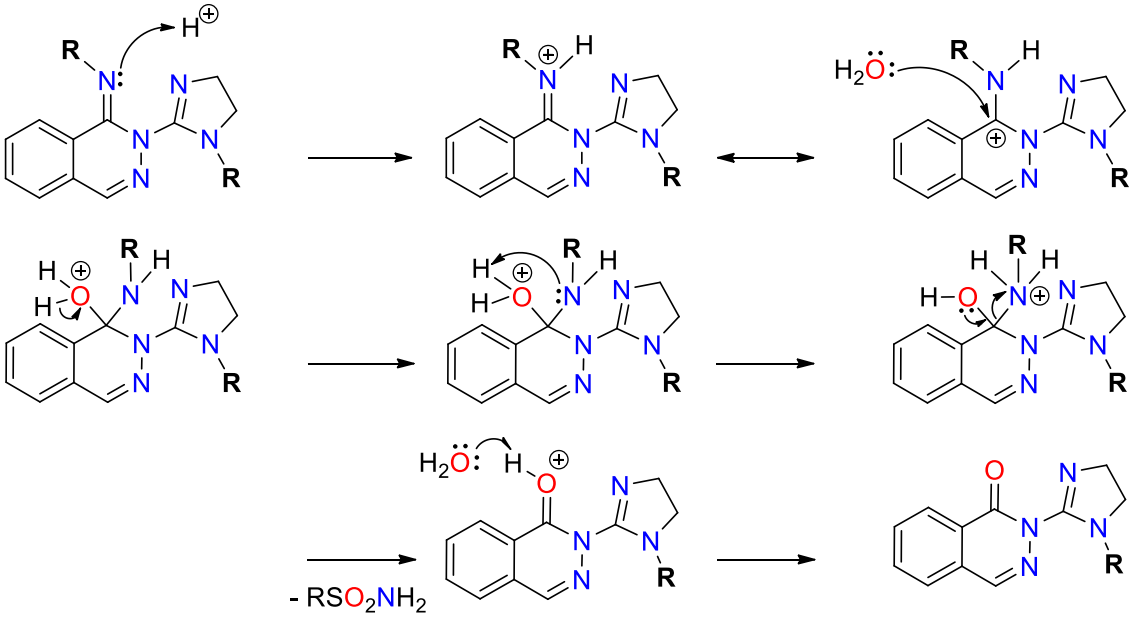
Results and discussion

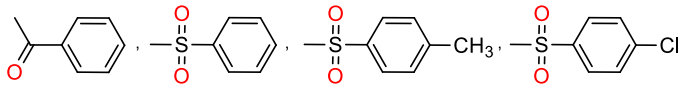
During the course of our experimental research and purification of compounds **V** and **VI** it was found that in the presence of water and traces of acid lead to the formation of phthalazin-1(2*H*)-one derivatives **VII** and **VIII**.



Results and discussion

The mechanism of the formation of phthalazin-1(2*H*)-ones **VII** and **VIIIa-c** may be explained as follows: The protonation of the nitrogen converts the imine group into iminium ion which as electrophilic species is attacked by water in the next step. Then, a proton transfer from the oxygen to the nitrogen gives rise to the formation of an oxonium intermediate which, after deprotonation, gives the desired phthalazin-1(2*H*)-one.

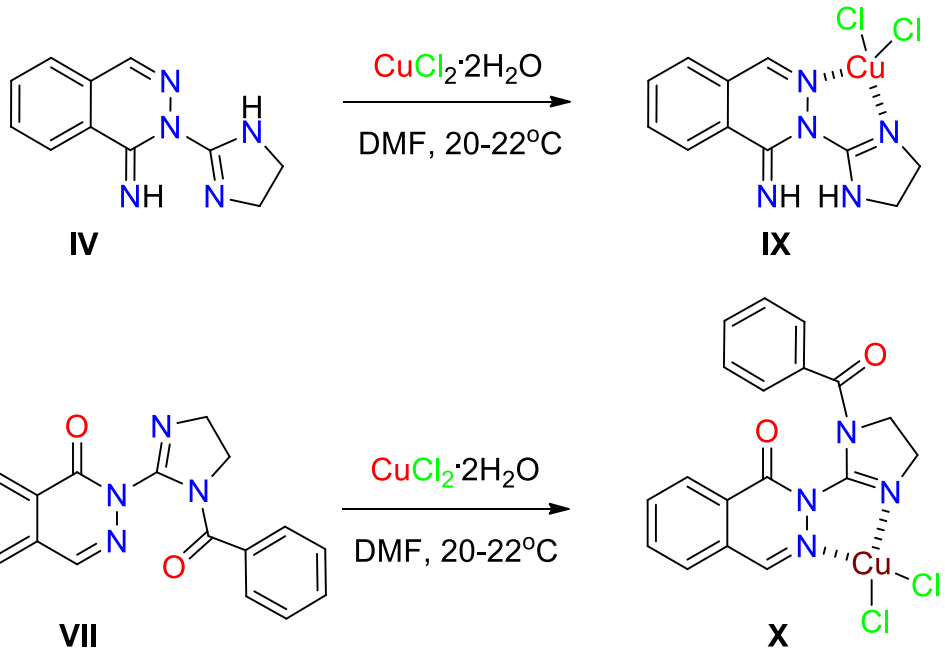


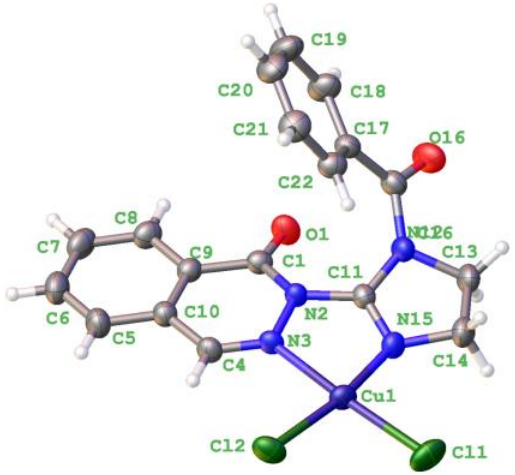
R = 

VII **VIIIa** **VIIIb** **VIIIc**

Results and discussion

Copper(II) complex of 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IX**) and 2-(1-benzoyl-4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-one (**X**) were prepared by reaction of copper(II) chloride dihydrate with ligands **IV** and **VII** in such 99% dimethylformamide.

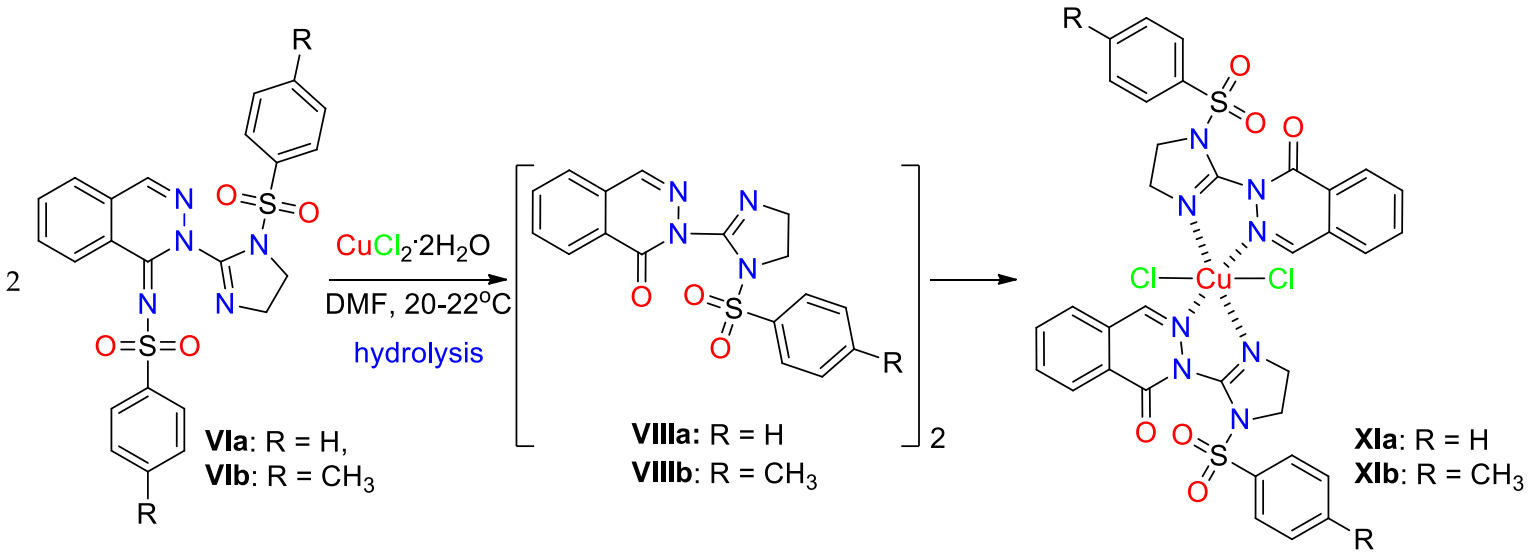




Crystallographic structure of copper(II) complex X

Results and discussion

During the course of experimantal research it was found that synthesis of copper(II) complexes with *N*-{2-[1-(arylsulfonyl)-4,5-dihydro-1*H*-imidazol-2-yl]phthalazin-1(2*H*)-ylidene}-benzenesulfonamides **VIa-m** has failed. It turned out that ligands **VI** in the presence of copper(II) ion are susceptible to the hydrolysis. As a result cooper(II) complexes with 2-[1-(arylsulfonyl)-4,5-dihydro-1*H*-imidazol-2-yl]phthalazin-1(2*H*)-ones are formed. Green crystals of copper(II) complexes **XIa** and **XIb** were obtained upon slow evaporation of the solvent over 14-21 days.



Complex XIa

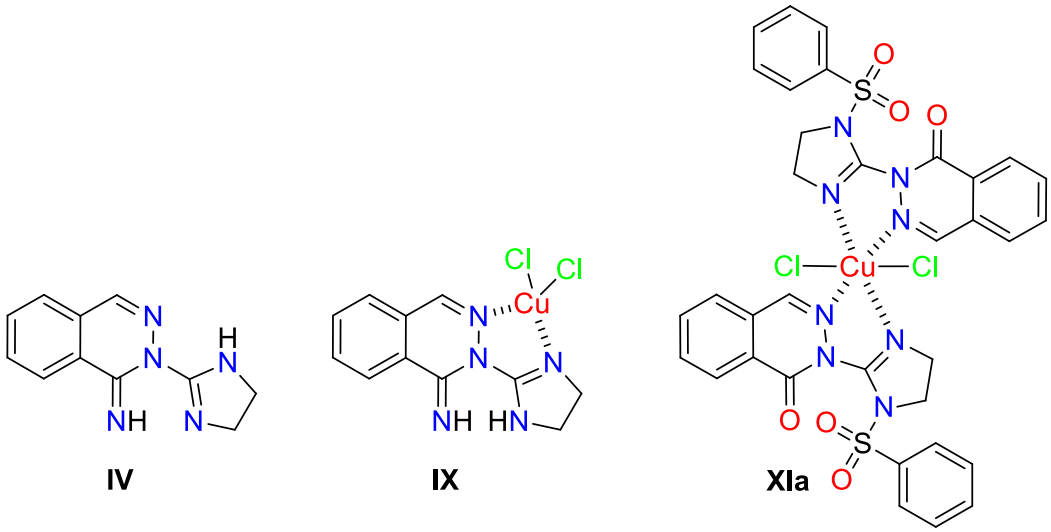
Complex XIb

Results and discussion

The *in vitro* cytotoxic activity of the copper(II) complexes **IX**, **XIa** towards the cervical cancer cell line (HeLa) have been investigated at the *Division of Pharmaceutical Biosciences*, *Faculty of Pharmacy*, University of Helsinki.

Tested compounds **IX** and **XIa** display pronounced antiproliferative activity with calculated IC_{50} values of **2.13 µM** and **12.87 µM**, respectively. Moreover, both complexes exhibit nontoxic effect against normal non-tumorigenic mouse fibroblasts BALB/3T3 (**IX**: IC_{50} = 135.30 µM and **XIa**: IC_{50} = 113.60 µM), which pointed towards their selectivity as a potential antitumor agents.

It should be pointed out, that corresponding free ligand 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IV**) was less active than its metal complex (IC_{50} = 87.74 µM).



Conclusions

1. Structures of the ligands and copper(II) complexes were confirmed by **IR**, **NMR spectroscopic data**, **elemental analysis**, as well as single crystal **X-ray analysis**.

2. The obtained compounds constitute a **small library** of heterocyclic compounds in the anticancer drugs design process.

3. The two tested copper(II) complexes exhibited pronounced **cytotoxic activity** against the cervical cancer cell line **HeLa**, and their calculated IC_{50} values were in the range of **2.13**-**12.87** μM.

4. The promising preliminary results are starting point for further biological studies toward the anticancer activity of newly prepared copper(II) complexes.

Acknowledgments

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The X-ray diffraction studies were carried out at the Crystallography Department, Faculty of Chemistry, Adam Mickiewicz University in Poznań, Poland.

The biological studies were performed at the Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, Finland.

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