

# GREEN SYNTHESIS AND ANTICANCER EVALUATION OF A BIPYRIDINE-COPPER(II) COMPLEX

Jakov Babić<sup>1</sup>, Mislav Vorkapić<sup>1</sup>, Tea Kozić<sup>1</sup>, Tomislav Balić<sup>1</sup>, Stjepan Šarić<sup>1</sup>, Elvira Kovač-Andrić<sup>1,\*</sup> and Nikolina Filipović<sup>1,\*</sup>  
<sup>1</sup>Department of Chemistry, University of Osijek, cara Hadrijana 8/a, 31000 – Osijek, Croatia  
 E-mail: [nfilipovic@kemija.unios.hr](mailto:nfilipovic@kemija.unios.hr)

## 1 INTRODUCTION

Cocrystals are gaining importance in drug development for modifying drug properties without altering their structure. A copper(II)-bipyridine complex was synthesized using green chemistry methods, emphasizing environmental sustainability. The complex showed strong cytotoxicity against Hep G2 cells, surpassing the activity of the free ligand and copper salt. These results highlight the value of ligand design and green synthesis in developing effective metal-based therapeutics (Fig.1)<sup>1,2</sup>.

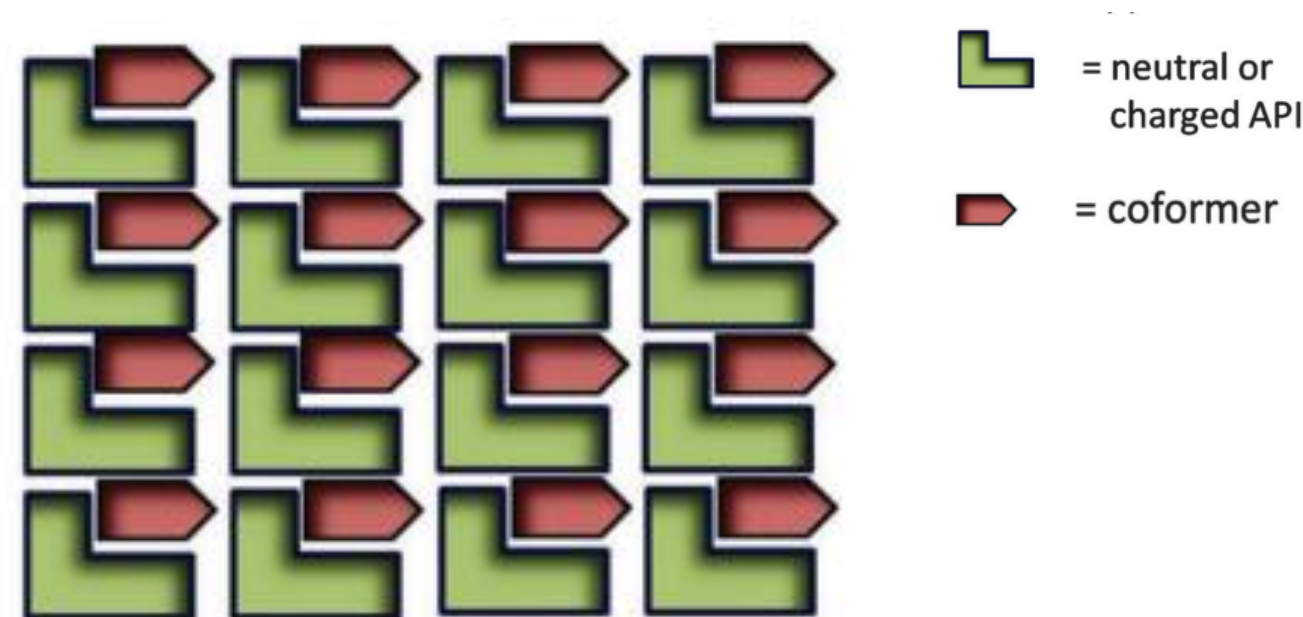


Fig. 1. Molecular cocrystal.

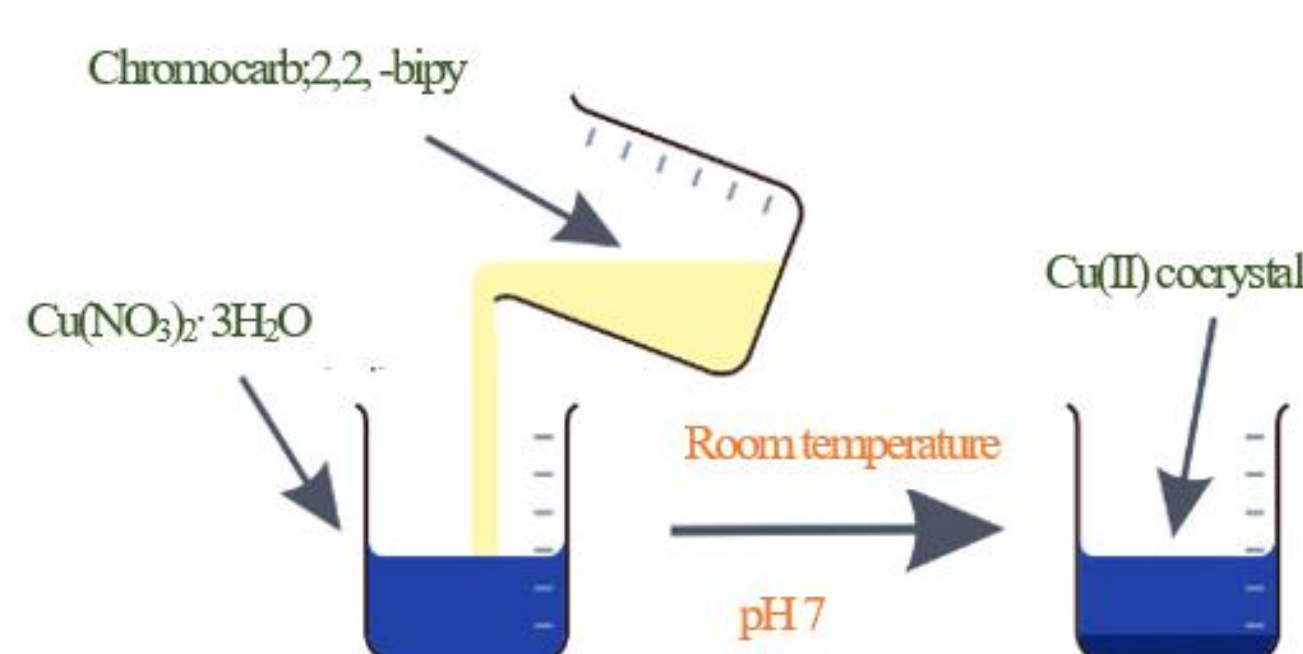
## 2 MATERIALS AND METHODS

### GENERAL PROCEDURE FOR PREPARATION OF COMPLEXES

In accordance with the principles of green chemistry, the copper(II) complex was synthesised using water and ethanol as environmentally friendly solvents. A 5 cm<sup>3</sup> aqueous solution (0.05 mmol) of copper(II) nitrate (prepared with ultrapure water) was combined with 10 cm<sup>3</sup> of a warm ethanolic solution (0.05 mmol each) of chromone-2-carboxylic acid (HL1) and 2,2'-bipyridine (L3). The reaction mixture was carefully stirred, and the pH was adjusted to 7 with 0.1 mol dm<sup>-3</sup> sodium hydroxide (Scheme 1).

### 2D MTT ASSAY

After synthesis, using classical solution chemistry in the stoichiometric ratio (1:1, metal:ligand), the compound was dissolved in DMSO (10<sup>-3</sup> mol/dm<sup>3</sup>) and subjected to cytotoxic appraisal (2D MTT assay). The compound and the ligands were tested on 7 cell lines (Fig.2.)



Scheme 1. Preparation the Cu(II) cocrystal.

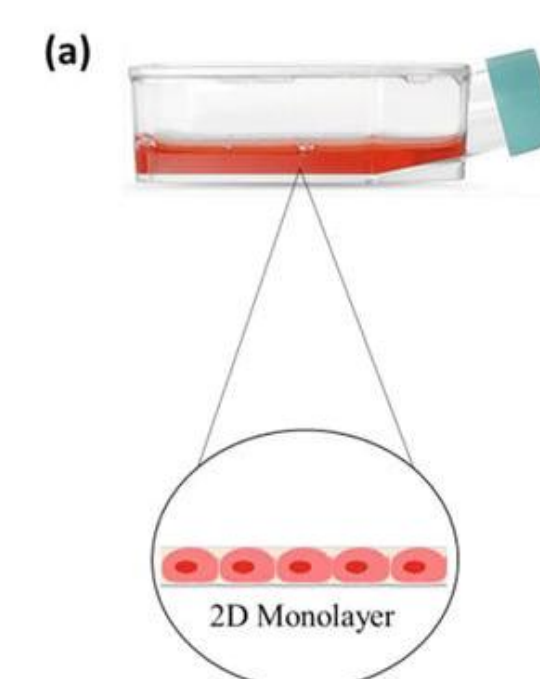


Fig. 2. 2D cell culture model - monolayer.

## 3 RESULTS

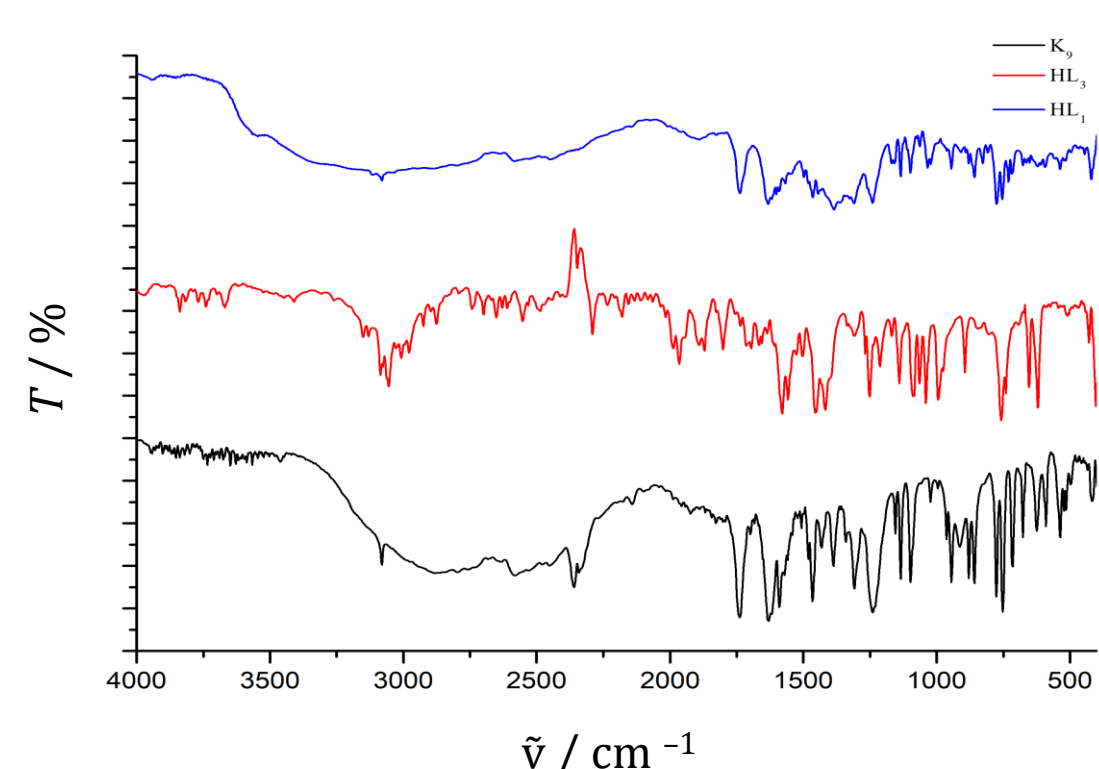
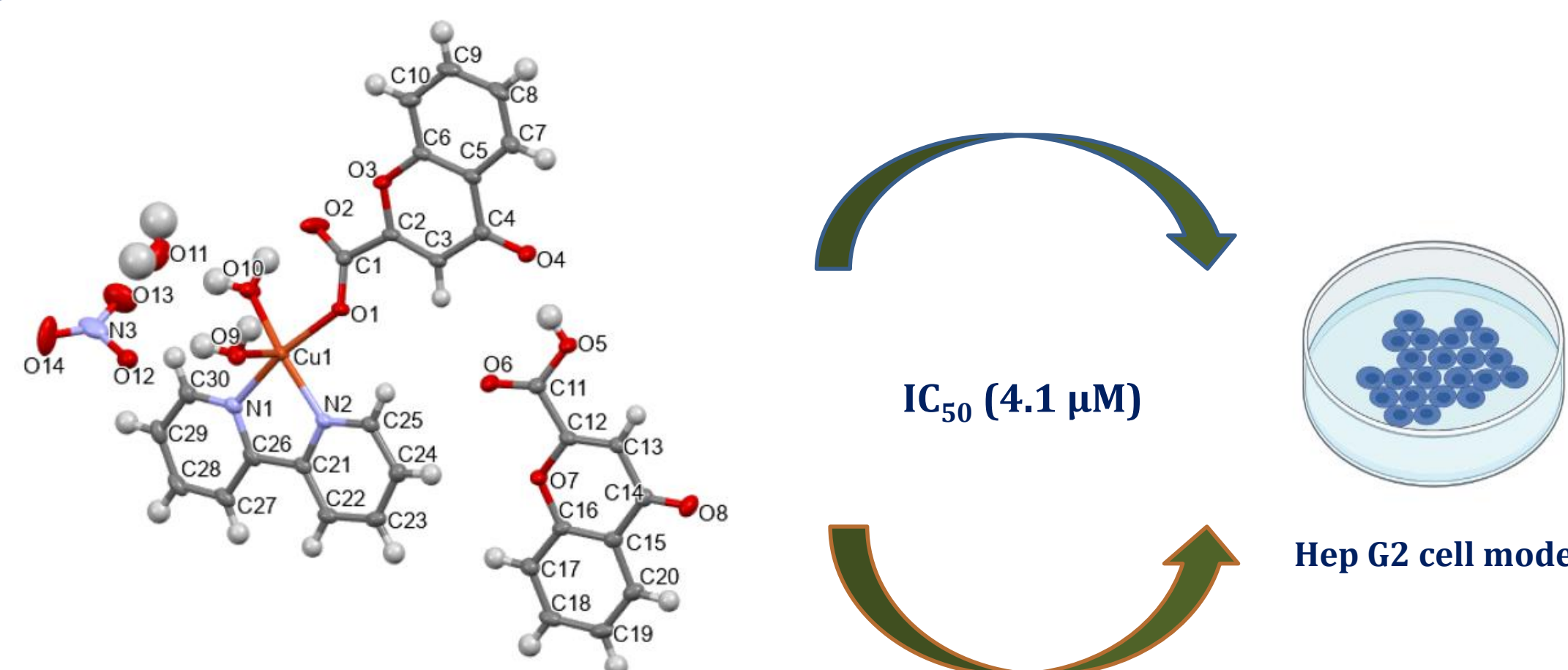


Fig. 3. Comparative IR spectra of ligands HL<sub>1</sub> (blue), L<sub>3</sub> (red), and compound K<sub>9</sub> (Cu-cocrystal) (black).



Scheme 2. Selectivity index (SI) and IC<sub>50</sub> value for copper(II) cocrystal on the Hep G2 cell line.

Table 1. Concentration of Cu(II) compound and ligands that exerts 50 % inhibition with respect to untreated cells.

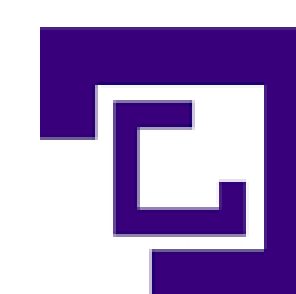
Cell lines	Cocrystal	Ligands
MDA - MB - 231	<20	<20
NCI - H358	11.6	<20
KATO III	<20	<20
Hep G2	4.1	<20
Caco - 2	1.1	<20
HT - 29	<20	<20
MRC - 5	<20	<20

## 4 Conclusions

A green synthesis using bipyridine and chromone-2-carboxylic acid led to a copper(II) complex with strong selectivity against Hep-G2 cells, demonstrating the potential of environmentally friendly methods for targeted cancer therapy.

### REFERENCES

- Yan, Y-L; Miller, M.T; Chao, Y; Cohen, M.S. Synthesis of hydroxypyrrone -based matrix metalloproteinase inhibitors: Developing a structure - activity relationship. *Bioorg. Medic.Chem.Lett.* 2009, 19, 1970-1976.
- Toso, L. et al. A family of hydroxypyrrone ligands designed and synthesized as iron chelators. *Jour.Inorg.Biochem.* 2013, 127, 220-231.



Third EUROPEAN  
GREEN  
CONFERENCE  
10-13 June 2023 Vodic, CROATIA