THE EFFECT OF COPPER(II) COCRYSTAL WITH HETEROCYCLIC LIGANDS ON THE VIABILITY OF THE CACO-2 CELL LINE

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1 Introduction

Cocrystals, a long-known but little-studied class of crystalline solids, have attracted the interest of scientists over the last decade and are now an integral part of the preformulation phase of drug development. The advantage of pharmaceutical cocrystals containing a drug molecule is the ability to modify the physicochemical properties without the need to covalently modify the drug molecule. Cocrystals have attracted attention as an alternative solid form in drug development (Fig.1).[1,2]

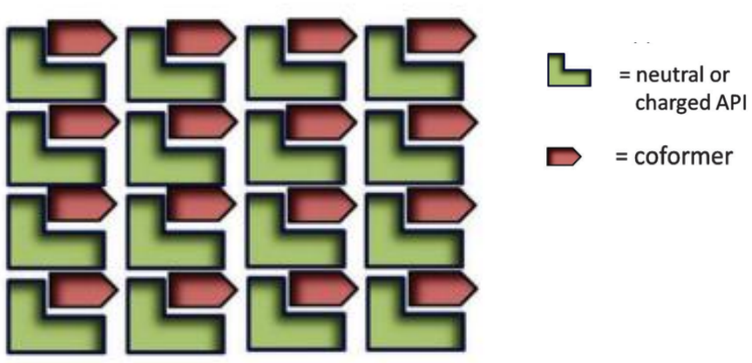


Fig. 1. Molecular cocrystal.

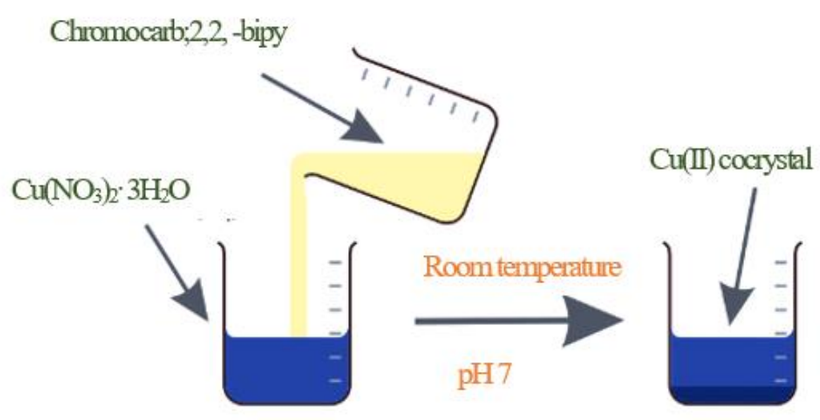
2 Materials and methods

GENERAL PROCEDURE FOR PREPARATION OF COMPLEXES

5 cm^3 of 0.05 mmol aqueous (ultrapure water) solution of copper(II) nitrate was mixed with 10 cm^3 of 0.05 mmol of warm ethanol solution of the chromone–2–carboxylic acid (chromocarb; HL_1) and 2,2′-bypridine (2,2′-bipy; L_3). After mixing, the final solution was neutralized with 0.1 mol dm^{-3} sodium hydroxide to pH 7 (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^{-3} mol/dm^3) 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.

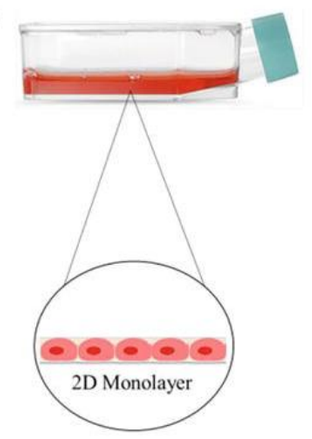


Fig. 2. 2D cell culture model - monolayer.

3 Results

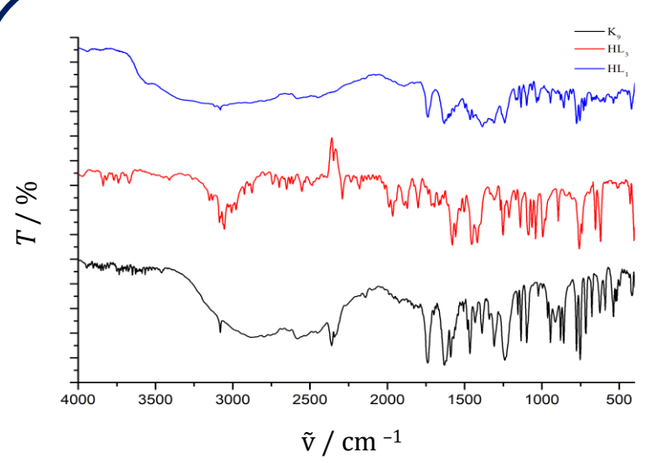
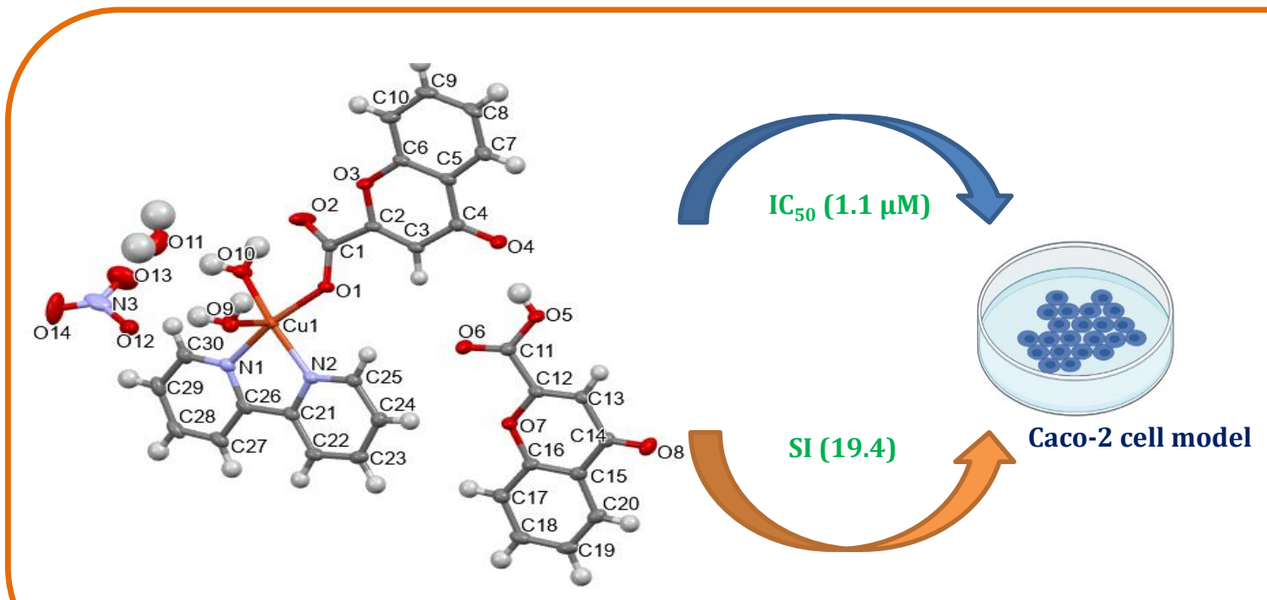


Fig. 3. Comparative IR spectra of ligands HL_1 (blue), L_3 (red), and compound K_9 (Cu-cocrystal)(black).



Scheme 2. Selectivity index(SI) and IC_{50} value for copper(II) cocrystal on the Caco-2 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

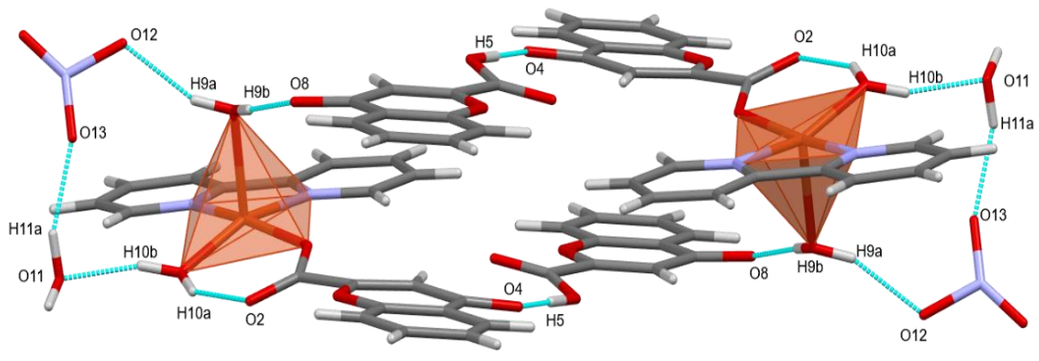
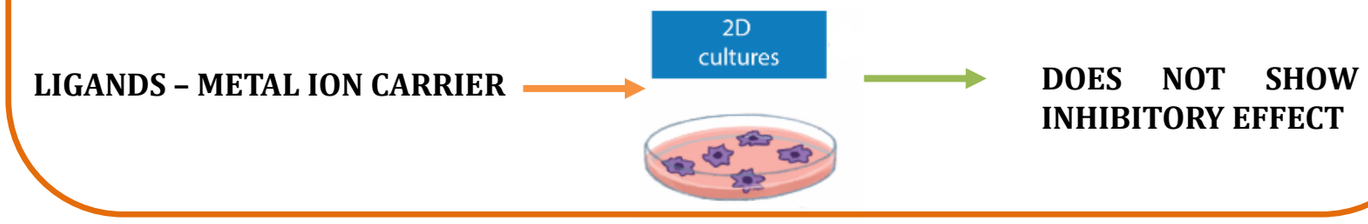


Fig. 4. Illustration of the intermolecular interactions in the copper(II) compound.



4 Conclusions

This mixture of two ligands yielded a compound highly specific for the Caco-2 cell line, inhibiting it by 94.8% at a concentration of 10^{-5} mol dm^{-3}. The knowledge gained from this research may contribute to the development of new, highly selective compounds.

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