CHEMISTRY

SYNTHESIS OF MIXED LIGAND COPPER (II) COMPLEX OF BENZIMIDAZOLE SCHIFF BASE WITH 1,10-PHENANTHROLINE AS POTENTIAL ANTITUMOR AGENT

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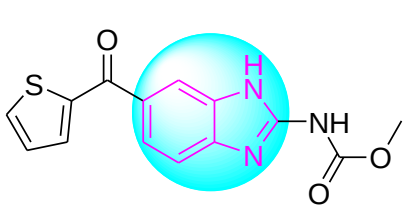
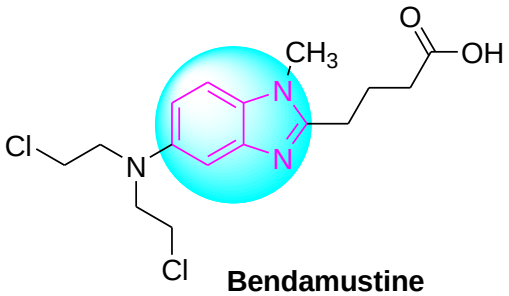
Abstract. *The field of mixed metal complexes containing benzimidazole and 1,10-phenantroline ligands was fast developing due to their advantageous attributes as potential drugs.*
In this work was shown the synthesis of a copper complex of Schiff base derivative of salicylidene-2-aminobenzimidazole and 1,10-phenantroline as potential antiproliferative agent. The structure of the chemical scaffolds was authenticated by IR, NMR, elemental analyses.
Keywords: *benzimidazoles, phenanthrolines, copper (II) complexes.*

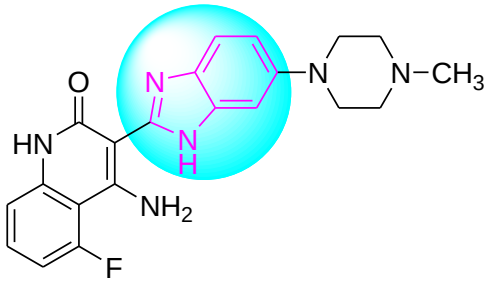
Introduction. Copper complexes are recently being investigated and combined with different heterocycle moieties to discover new drugs since among the metals, copper is an endogenous metal rather than an exogenous and thus less toxic, it is selectively permeable to membranes of cancer cells and their level is delicately regulated in cells and last but not least the copper has considerable redox and DNA cleavage potentials [1]. The benzimidazole moiety itself has a number of biological activities (antimicrobial, antifungal, anthelmintic, antiviral, antihypertensive, antihistaminic, anti-inflammatory, anti-ulcer) including and anti-cancer potential and it has been used as privileged scaffold to synthesize a number of antitumor drugs as nocodazole, bendamustine, dovitinib (Fig. 1) etc. [2].



Nocodazole



Bendamustine



Dovitinib

Fig. 1. Antitumor drugs having benzimidazole moiety.

On the other hand, among different heterocyclic compounds, the phenantrolines are also well-known and important substructures with different biological and pharmacological properties. Their metal complexes as well as supramolecular self-assembly structures show a variety of biological activities, principally antimicrobial [3, 4] and antitumor [5, 6].

Hussain et al. [7] were reported on the synthesis of three copper complexes with benzimidazole-derived scaffolds and secondary ligands 1,10-phenanthroline and 2,2′-bipyridine. The new complexes were tested for biological studies, i.e., anticancer as well as NSAIDS. *In vitro* cytotoxicity results against MCF-7 human breast cancer cell lines were showed the profound potential of $[Cu(BImSB)(Phen)(H_2O)]NO_3$ in comparison to the complexes $[Cu(BImSB)_2]$ and $[Cu(BImSB)(Bpy)(H_2O)]NO_3$, wherein BImSB is Schiff base ligand derived from 2-aminobenzimidazole and o-vanillin, Phen is 1,10-phenantroline and Bpy is 2,2′-bipyridine. In our utility model BG3969U1 [8], we described on the design and self-assembly synthesis on molecular complex with formulae: $(phen)(1\text{-methyl-2-amino-Bz})_2H^+BF_4^-.1/2H_2O$ by linking the main structural unit of the 2-amino-1-methylbenzimidazole (1-methyl-2-amino-Bz) ring system with the 1,10-phenantroline (phen) and examined its antitumor activities *in vitro* against two human breast cancer cell lines MCF-7 and MDA-MB-231. Encouraged by these promising results, I report here the synthesis of novel copper (II) mixed-ligand complex as potential antitumor agent.

Aim. The aim of the present study is synthesis and characterization of novel copper (II) complex incorporating benimidazole and 1,10-phenantroline ligands, as potential anticancer agent.

Material and Methods. 2-Aminobenzimidazole, 2-hydroxybenzaldehyde (salicylicaldehyde), $Cu(NO_3)_2{\cdot}3H_2O$, 1,10-phenanthroline, acetic acid, all the solvents were used as purchased from the companies Sigma-Aldrich and Alfa Aesar without further purification. Infrared spectra (in KBr) were recorded with a Varian apparatus. 1H-NMR spectra were taken on a Bruker Avance AV 600 (Bruker, Faelanden, Switzerland) using deuterated DMSO as solvent. The elemental analysis (C, H, N) were performed on a Perkin-Elmer elemental analyzer. Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical value.

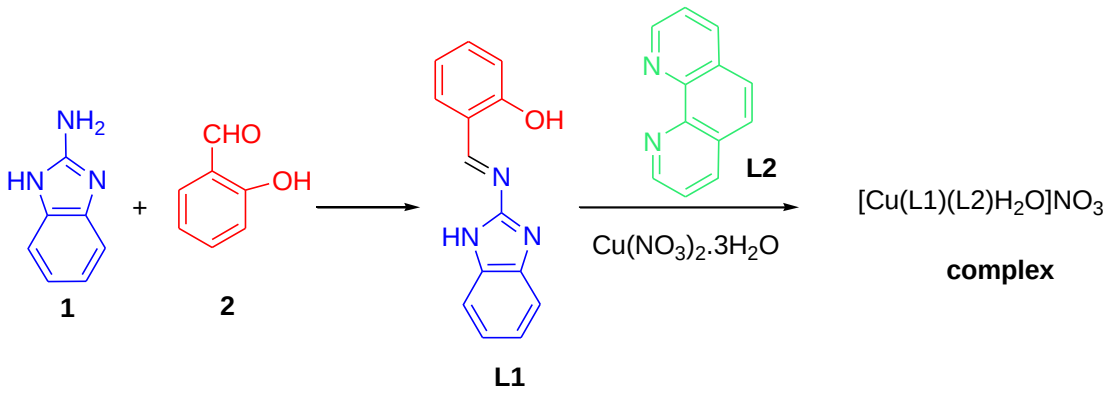
2-*((1H-benzo[d]imidazol-2-ylimino)methyl)phenol (L1)*

The synthesis of ligand **L1** was carried out by condensation reaction between 2-aminobenzimidazole and 2-hydroxybenzaldehyde as reported earlier [9]. The chemical structure of the Schiff base was confirmed by comparison with the reported melting point and NMR chemical shifts [10].

Synthesis of complex $[Cu(L1)(L2)(H_2O)]NO_3$. Complex was prepared by a synthetic procedure [7] in which a 0.101 g (0.42 mmol) $Cu(NO_3)_2.3H_2O$ in 6 mL aqueous methanol (1:1 v/v) was reacted with 0.083 g (0.42 mmol) 1,10-phenantroline.H_2O (L2) while stirring at room temperature for 0.5 h followed by addition of methanolic solution of 2-((1*H*-benzo[d]imidazol-2-ylimino)methyl)phenol (L1) (0.100 g, 0.42 mmol). The reaction mixture was stirred for 4 h, and then the green precipitate was filtered, washed with and cold methanol followed by drying in vacuum. Yield – 73%. Anal. calcd. for $C_{26}H_{20}N_6O_5Cu$ (C, H, N): Calculated (%): C, 55.76; H, 3.60; N, 15.01; Found (%):C, 55.40; H, 3.57; N, 14.89.

Results and discussion.

The preparation of azomethines (Schiff bases) of benzimidazol-2-ylamines can be carried out: by heating an ethanolic solution of equimolecular amounts of aldehyde and 2-aminobenzimidazole (method A); addition of a 5-10% aqueous solution of alkali to a solution of the two components in alcohol (method B); and grinding aldehyde and 2-aminobenzimidazole with a small amount of 5-10% aqueous alkali (method C). While carrying out the reaction by method A usually requires heating, when methods B and C are used the reaction complete even in the cold [11]. A. Nowicka et al. were obtained benzimidazole Schiff base derivatives in boiling ethanol with the presence of catalytic amounts of Triflate (method C) [10] as well as in a mixture of absolute ethanol/benzene (5:1) in the presence of catalytic amounts of glacial acetic acid (method D) [12]. Schiff bases L1 was obtained in the reaction of 2-aminobenzimidazole with salicylic aldehyde according method A [9] in ethanol (Scheme 1). The mixture was refluxed for about 5 hours. The compound prepared was purified by recrystallization from ethanol and its chemical structure was confirmed by IR, ^1H NMR spectral data.



*Scheme 1. Reaction scheme for preparation of the Schiff base ligand **L1** and copper (II) complex.*

Target copper (II) complex was prepared in high yield from reactions of 2-((1*H*-benzo[d]imidazol-2-ylimino)methyl)phenol – ligand (L1) with copper (II) nitrate trihydrate and 1,10-phenantroline, as co-ligand (L2) in 1:1:1 ratio. The formula of the complex $[Cu(L1)(L2)(H_2O)]NO_3$ was determined by elemental analysis.

Conclusions. Schiff base ligand (L1) was successfully synthesized from 2-aminobenzimidazole and salicylaldehyde and used for preparation of copper (II) complex with the participation of $Cu(NO_3)_2.3H_2O$ and 1,10-phenantroline (L2). Similarly to previously report mixed ligand copper (II) complexes of benzimidazole I expect the synthesized above complex to exhibit anti-cancer activity.

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