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# In vivo anticancer, anti-inflammatory, and toxicity studies of mixed-ligand Cu(II) complexes of dien and its Schiff dibases with heterocyclic aldehydes and 2-amino-2-thiazoline. Crystal structure of [Cu(dien)(Br)(2a-2tzn)](Br)($H_2O$)

A.Th. Chaviara [a], P.C. Christidis [b], A. Papageorgiou [c], E. Chrysogelou [c], D.J. Hadjipavlou-Litina [d], C.A. Bolos [a,*]

[a] *Laboratory of Inorganic Chemistry, Department of Chemistry, Aristotle University, Thessaloniki 54124, Greece*
[b] *Laboratory of Applied Physics, Aristotle University, Thessaloniki 54124, Greece*
[c] *Department of Experimental Chemotherapy, Symeonidion Res. Center, Theagenion Cancer Hospital, Al. Simeonides 2 Str., Thessaloniki 54007, Greece*
[d] *Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece*

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**Abstract**

A new series of complexes of the type [Cu(dien)(2a-2tzn)$Y_2$] and [Cu(dienXX)(2a-2tzn)$Y_2$], where dien = diethylenetriamine and dienXX = Schiff dibase of diethylenetriamine formed with 2-furaldehyde (dienOO), 2-thiophenecarboxaldehyde (dienSS), or pyrrol-2-carboxaldehyde (dienNN); Y = Cl, Br or $NO_3$; and 2a-2tzn = 2-amino-2-thiazoline, were synthesized and their structure established by C, H, N and Cu analysis; IR and electronic spectra; magnetic susceptibility; and molar conductivity. The isolated complexes are monomers, paramagnetic, and electrolytes of types 1:1 or 1:2. In both types of solid state complexes, [Cu(dien)(2a-2tzn)$Y_2$] and [Cu(dienXX)(2a-2tzn)$Y_2$], dien and its Schiff dibases are bonded to Cu(II) in a tridentate fashion through 3N atoms. The coordination sphere is completed by the endocyclic nitrogen of the thiazoline moiety and by two Cl, Br, or $NO_3$ groups with distorted octahedral geometry. The proposed structure of these compounds was supported by X-ray analysis of [Cu(dien)(Br)(2a-2tzn)](Br)($H_2O$). The coordination polyhedron around the copper atom can be described as a distorted square pyramid $[Cu(dien)(Br)(2a\text{-}2tzn)]^+$. Its basal plane is occupied by the four nitrogen atoms of the dien and thiazoline ligands with Cu–N distances ranging between 1.996(6) and 2.032(3) Å, and the axial position is occupied by one of the two bromine atoms (Br1) with a Cu1–Br1 bond distance of 2.782(1) Å. The second bromine atom (Br2) is 4.694(2) Å from the copper atom, which exists as a discrete anion and is responsible for the cationic nature of the complex. Results regarding toxicity, antitumor, and anti-inflammatory activities of the investigated compounds are promising and allow the selection of a lead compound for further biological studies.


*Keywords:* 2-Amino-2-thiazoline; Complexes; Cu(II); Toxicity; Antitumor; Anti-inflammatory; X-ray crystallography

## 1. Introduction

Although numerous organic, inorganic, or coordination compounds with antiproliferative activity have been reported [1–3] most of them are excluded from further clinical studies due to their toxicity, causing numerous undesirable side effects. Evidently, toxicity should be among the criteria that should be examined before studies of biological activity are undertaken. Continuing our work [4–6] on the biological activity of Schiff dibase compounds with S,N-heterocyclic adducts we report

* Corresponding author. Tel.: +302310997705; fax: +302310997738.
*E-mail address:* bolos@chem.auth.gr (C.A. Bolos).

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the synthesis of a new series of Schiff dibase compounds with 2-amino-2-thiazoline (2a-2tzn), to be of special interest thanks to their antibiotic, anti-inflammatory [7], antifungal [8], anticonvulsant, local anesthetic, fungicidal, bactericidal, herbicidal, insecticidal, antitubercular, cardiotonic, acaricidal, antiulcer, antineoplastic [9–11] and antihypertensive [12] properties.

The biological activity of 2a-2tzn can be attributed to its coordination with either protein constituents [12] as a simple organic compound or to metalloelements in mixed-ligand complexes. Furthermore, many of the anti-inflammatory drugs used to date are non-steroidal, usually aromatic, and/or heterocyclic compounds with various substituents on the aromatic or heterocyclic ring, e.g., 2-(acetyloxy)benzoic acid, 2-carboxyphenyl esters, and 4-(acetylamino)phenyl [13]. Most NSAIDs, non-steroidal anti-inflammatory drugs, are weak acids with p$K_a$ values ranging from 3 to 5 [14] and their side effects are suggested to be connected to their acidic character [15]. There is increased interest in the development of effective non-acidic anti-inflammatory agents among which basic NSAIDs copper complexes are gaining interest because of their improved pharmacological properties as well as reduced gastric toxicity. Copper complexes of many several ligands have been prepared and evaluated for anti-inflammatory activity and irritancy after oral, subcutaneous, and local administration in rats and guinea pigs. Other compounds known for their anti-inflammatory properties are the S,N-heterocyclic ligands, e.g., thiazoline and its derivatives [16,17]. The Cu(II) thiazoline complexes are anticipated to yield agents with enhanced anti-inflammatory activity and reduced gastro-intestinal (GI) toxicity, compared to the uncomplexed ligands.

Herein, we report the synthesis and spectroscopic characterization of a new series of Cu(II) complexes of dien Schiff dibase and thiazoline ligands. The successful reaction of the new compounds with guanosine prompted us to proceed with biological studies including toxicity, antitumour, and anti-inflammatory activities of these compounds.

## 2. Experimental

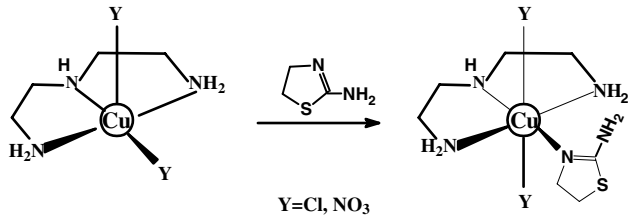
All chemicals were purchased from Aldrich, EDH Chemicals, and Merck (reagent grade) and used without further purification.

### 2.1. Syntheses of the copper(II) chelates

The new compounds were prepared by the reaction of the starting materials [Cu(dien)$Y_2$] and Schiff dibase complex [Cu(dienXX)$Y_2$] [18,19,6] with 2a-2tzn. The general procedures are given below.

#### 2.1.1. [Cu(dien)(2a-2tzn)$Y_2$]

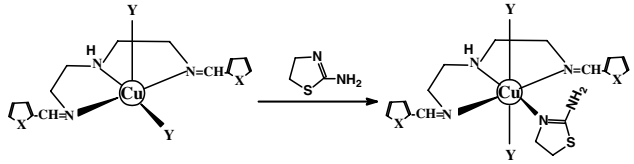
To a suspension of Cudien$Y_2$ (2 mmol) in MeOH (20 mL), a 10 mL methanolic solution of 0.204 g (2 mmol) of 2a-2tzn was added dropwise. After stirring for 12 h at room temperature, both the starting material and 2a-2tzn dissolved. The blue solution was then filtered to remove any insoluble material and ether was added slowly until the clear solution became cloudy. After staying for 24 h at 5 °C the solid product shown below, was isolated by filtration, washed with ether, and dried in air.




The reaction of Cudien$Br_2$ with 2a-2tzn, performed in a similar manner, affords the compound [Cu(dien)-(Br)(2a-2tzn)](Br)($H_2O$).

#### 2.1.2. [Cu(dienXX)(2a-2tzn)$Y_2$]

Ten millimoles of a heterocyclic aldehyde; 2-thiophenecarboxaldehyde, 2-furaldehyde, or pyrrol-2-carboxaldehyde, was stirred with 0.55 mL (5 mmol) of dien at ice bath temperature. The resulting syrup-like Schiff dibase was diluted with 20 mL of methanol, and another methanolic solution (10 mL) of 5 mmol $CuCl_2 \cdot 2H_2O$, $CuBr_2$, or $Cu(NO_3)_2 \cdot 3H_2O$ was added over a period of 30 min. After that, a solution of 0.506 g (5 mmol) of 2a-2tzn in 10 mL of methanol was added slowly. The solid products, illustrated below, were isolated by filtration, washed with ether several times, and dried at room temperature.




### 2.2. Physical measurements and determinations

Carbon, hydrogen, and nitrogen analyses were performed in our microanalytical laboratory with a Perkin–Elmer 240B microanalyser instrument, whereas copper analyses were performed with a Perkin–Elmer model 403 Atomic Absorption Spectrometer, equipped