MATERIALS BASED ON QUINOLINE SULFONAMIDE - METALS WITH ANTIMICROBIAL ACTIVITY AND THEIR X-RAY CHARACTERISATION

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Abstract

Quinoline sulfonamide complexes with different metals represent a new class of materials of great interest especially for their fotoluminiscent and biological activity (mostly antibacterial and antifungal activity). The emphasis of this work was to synthesize, characterize through X-ray and determine the antibacterial and antifungal proprieties of newly materials for medicinal chemistry applications based on **Q**uinoline **S**ulfonamide **C**omplexes **M**etals (**QSCM**). The synthesis of the **QSCM** materials is straight and efficient, in two steps: acylation of aminoquinoline followed by complexation with M^{2+} metal (Zn^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}). The synthesized quinoline sulfonamide complexes M^{2+} metals were characterized by X-ray diffraction on single crystal and by FTIR and NMR spectroscopy. The X-ray spectra prove unambiguously the structure of complexes, e.g for the Zn (II) complex crystallize in the monoclinic P21/n space group type, with *a*= 1.21602(5) nm, *b* = 1.55478(5) nm, *c* = 1.61786(6) nm, *α* = 90°, *β* = 106.007(2)°, *γ* = 90°, *V*= 2.9402(19) $nm^3$and *Z* = 4.Sulfonamide acts as bidentate ligand trough *Zn-N*quinoline and *Zn-N*sulfonamide bonds, with atetrahedral coordination environment for Zn^{2+}. The **QSCM**M^{2+} complexes were tested for their antibacterial and antifungal activity, having a good antibacterial activity against gram positive germ*Staphylococcus aureus*,andgram negative germ *Escherichia coli*, and an excellent antifungal activity against fungus *Candida albicans*.

Keywords: X-Ray, quinoline sulfonamide complexes, M^{2+} transitional metals, antibacterial, antifungal

1. INTRODUCTION

Quinoline and its derivatives are privileged structures in medicinal chemistry, having a wide range of biological activities such as antimalarial, antitubercular, antiviral, antibacterial, antifungal, anticancer, etc. [1-6]. On the other hand sulfonamides are well known derivatives with antibacterial activity [7,8].The merge of the two moieties, quinoline and sulfonamide, followed by complexation with different metals, are leading to an interesting new class of compounds, namely quinoline sulfonamide complexes **QSCM**. The **QSCM** derivatives pay a particularly attention on scientific community during the last few years, especially for their fotoluminiscent [9-12] and biological properties. As far for biological properties, these compounds were found to have several activities, these including antiprotozoals and antimalarial and also antibacterial and antifungal activity [13-15].

In the light of the above consideration and encouraged by our recent results in the field of (di)azine with antimicrobial activity [4-6, 15], we report here the design, synthesis, X-ray characterization and antimicrobial activity of some hybrid quinoline – sulfonamide complexes.

2. RESULTS AND ITS DISCUSSION

In a preliminary communication [15] we show a straight and efficient method for synthesis of quinoline – sulfonamide complexes derivatives. Thus, in order to synthetise our hybrid **QSCM** derivatives we performed an initially acylation of aminoquinoline **1** with 4-chlorobenzene-1-sulfonyl chloride **2**, when the key intermediary

N-(quinoline-8-yl)-4-chloro-benzenesulfonamide **3** is obtained. The subsequent complexation of **3** with M^{2+} metal (Zn^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}) are leading to the disered compounds, the hybrid quinoline sulfonamide complexes **QSCM 4a-d**, **Figure 1**.

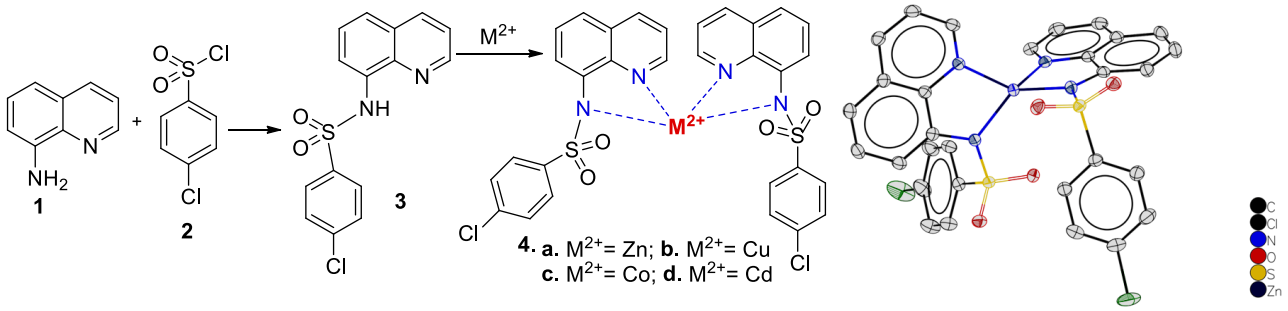

Figure 1 Reaction pathway and X-Ray structure (M^{2+}=Zn) for **QSCM** M^{2+} complexes

The structures of compounds were proven by elemental and spectral (IR, NMR, MS, X-Ray) analyses. Thus, if we consider the case of compound [Zn(*N*-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$] **4a** as representative for the **QBCM** complexes series, the X-ray structural analysis prove ambiguously the molecular structure (**Figure 2**), the main crystal data of **4a** being listed in **Table 1** and **Table 2**. The yellowish green crystals of thecomplex **4a** was obtained from methanol and crystallize in the monoclinic P21/n space group type, with a = 1.21602(5) nm, b = 1.55478(5) nm, c = 1.61786(6) nm, α = 90°, β = 106.007(2)°, γ = 90°, V = 2.9402(19) nm^3 and Z = 4. A summary of the main crystallographic data together data collection and refinement details are listed in **Table 1**, while selected bond lengths (nm), bond angles (°) and torsion angles (°) are listed in **Table 2**.

Table 1 Summary of crystal parameters, data collection and refinement of **QBCM** complex [Zn(N-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$] **4a**

Empirical formula	**$C_{30}H_{20}Cl_2N_4O_4S_2Zn$**
Formula weight	700.89
Temperature (K)	293(2)
ρ_{calc}g/cm^3	1.583
μ/mm^{-1}	4.534
F(000)	1424.0
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection (°)	8.042 to 141.616
Index ranges	-14 ≤ h ≤ 14, -19 ≤ k ≤ 10, -19 ≤ l ≤ 16
Reflections collected	10835
Independent reflections	5539 [R_{int} = 0.0147, R_{sigma} = 0.0170]
Data/restraints/parameters	5539/0/388
Goodness-of-fit on F2	1.040
Final R indexes (I>=2σ (I))	R_1 = 0.0286, wR_2 = 0.0752
Final R indexes (all data)	R_1 = 0.0297, wR_2 = 0.0761

From the X-ray structure presented in **Figure 2**and **Table 2**, we may notice that the sulfonamide acts as bidentate ligand with a distorted tetrahedral coordination environment for Zn^{2+}. The Zn-ligand bonding take place trough Zn-*N*quinoline and Zn-*N*sulfonamide bonds.The Zn-Nquinoline bond lengths (0.20426 and 0.20299 nm) are slightly larger than Zn-Nsulfonamide bonds (0.19729 and 0.19883 nm) but in an acceptable range as reported by other authors for similar complexes [9,20]. The bond lengths between nitrogen and sulfur

atoms from sulfonamide moiety (N2-S1= 0.15993 nm, N4-S2= 0.15883 nm) and between nitrogen atoms from sulfonamide and corresponding quinoline carbon (N2-C8= 0.1398 nm, N4-C23= 0.1406 nm) are typical for these sort of bonds.

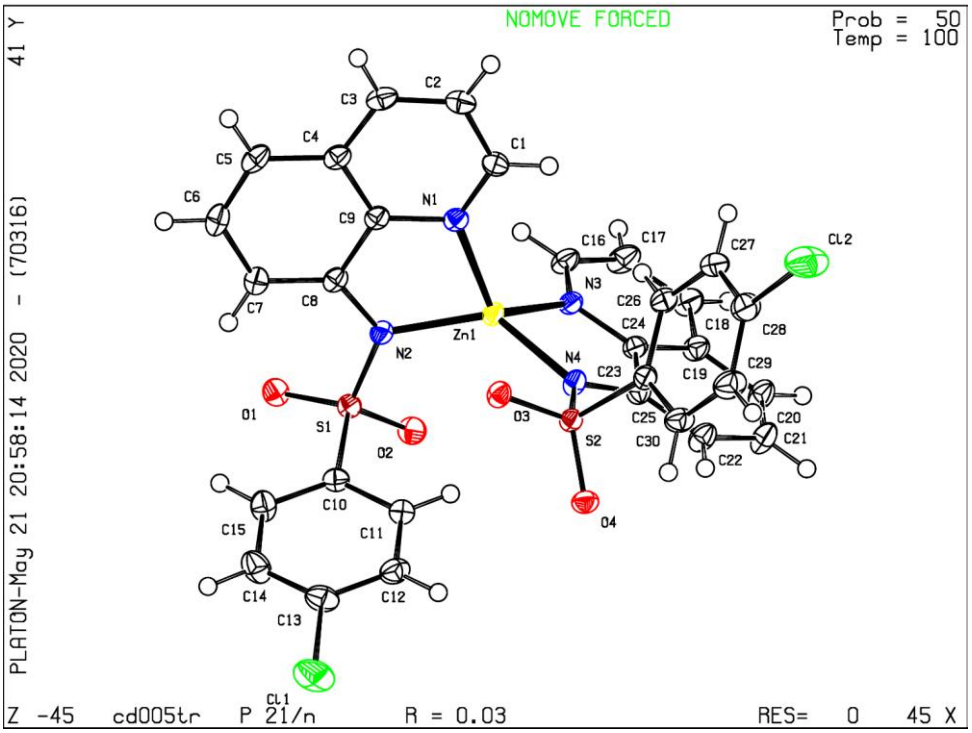

Figure 2 Molecular structure of **QBCM** complex [Zn(N-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$] **4a** including atom numbering scheme

The bond angles on the coordination environment of Zn^{2+} confirm the distorted tetrahedral coordination of metals, having values closely to 120^o (N3-Zn-N1 and N4-Zn-N1), 127^o (N2-Zn-N3 and N2-Zn-N4) and 82^o (N2-Zn-N1 and N4-Zn-N3). These situation it is also confirmed by the torsion angles on the coordination place of Zn^{2+}, having values for torsion angles Zn-N-C-C closely to 180^o or 0^o with the exception of angles Zn-N2-C8-C7 and Zn-N2-C8-C9 which have the values of 174.44^o respectively 5.93^o, **Table 2**.

Table 2 Selected bond lengths (nm), bond angles (^{o}) and torsion angles (^{o}) for **QBCM** complex **4a**

Bond lengths (nm)	Bond angles (^{o})	Torsion angles (^{o})
Zn-N1, 0.20426 (15)	N2-Zn-N1, 82.68 (6)	Zn-N1-C1-C2, 179.55 (13)
Zn-N2, 0.19729 (15)	N2-Zn-N3, 126.03 (6)	Zn-N1-C9-C4, 179.22 (13)
Zn-N3, 0.20299 (15)	N2-Zn-N4, 129.47 (6)	Zn-N1-C9-C8, 1.62 (18)
Zn-N4, 0.19883 (14)	N3-Zn-N1, 120.69 (6)	Zn-N2-C8-C7, 174.44 (15)
S1-N2, 0.15993 (15)	N4-Zn-N1, 121.50 (6)	Zn-N2-C8-C9, 5.93 (18)
S2-N4, 0.15883 (14)	N4-Zn-N3, 81.89 (6)	Zn-N3-C16-C17, 179.82 (15)
N2-C8, 0.1398 (2)	-	Zn-N3-C24-C19, 179.97 (14)
N4-C23, 0.1406 (2)	-	Zn-N3-C24-C23, -0.6 (2)
-	-	Zn-N4-C23-C22, 179.96 (16)
-	-	Zn-N4-C23-C24, 2.84 (19)

The antimicrobial activity of **QSCM** M^{2+} complexes was evaluated against gram-positive bacteria *Staphylococcus aureus ATCC 25923*, gram-negative bacteria *Escherichia coli ATCC 25922* and fungus *Candida albicans ATCC 10231*, by the Kirby-Bauer disk diffusion method [24]. Penicillin, Carbenicillin and Nystatin were used as positive control (C^+) for *S. aureus*, *E. coli* respectively *C. albicans*. The obtained results are expressed as diameters of inhibition zones (mm), the larger the diameter of the inhibition zones is the more active is the compound. The **QSCM** M^{2+} complexes have a good antibacterial activity against gram positive germ *S. aureus* (in the range of 11-21 mm) and gram negative germ *E. coli* (in the range of 12-19 mm). Against fungus *C. albicans* the **QSCM** M^{2+} complexes have an excellent antifungal activity(in the range of 12-25 mm), superior to control Nystatin (18 mm).

3.1. Materials and Methods

All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus (MELTEMP II) and are uncorrected. Analytical thin-layer chromatography (TLC) was performed with commercial Merck silica gel 60 F254 plates and visualized with UV light (λ_{max} = 254 or 365 nm). The structure of complexes was determined with an Agilent SuperNova Dual single crystal diffraction instrument. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction [17]. The structures were solved by direct methods using Olex2 [21] software with the SHELXS structure solution program and refined by full-matrix least-squares on F^2 with SHELXL-97 [19]. Atomic displacements for non-hydrogen atoms were refined using an anisotropic model. Hydrogen atoms were placed in fixed, idealized positions and refined as rigidly bonded to the corresponding atoms. The experimental setup procedure for synthesis of quinoline sulfonamide complexes as well as the detailed antimicrobial assay was described elsewhere [15].

3.2. Crystal Structures Determination

X-Ray analysis was recorded with an Agilent SuperNova Dual diffractometer equipped with a Mo/Cu (Kα radiation) fine-focus sealed X-ray tube and a graphite monochromator. A suitable crystal was selected and mounted on a hair thread and inserted into the four-circle SuperNova single crystal diffraction instrument. Intensity data were collected using Cu-Kα radiation (λ = 0.154184 nm), the crystal was kept at 100°K (-173.15°C) during data collection. A number of 5539 reflections from a total of 10835 acquired in 2.8345<θ<70.8363 range were used for refinement and structure solution. All H atoms were located in difference electron density maps and were included in idealized positions in a riding model with isotropic thermal parameters equal to 1.2 times those of their parent atoms. In the final cycles of refinement, least-squares weights of the form $w = 1/[\sigma^2(Fo)^2 + (0.0387P)^2 + 0.0691P]$, $P = (Fo^2 + 2Fc^2)/3$ were employed. Main crystallographic data together with refinement details for [Zn(*N*-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$] **4a** are listed in **Table 1** and **Table 2**.

4. CONCLUSION

We presented herein the design, synthesis, X-ray characterization and antimicrobial activity of some hybrid quinoline – sulfonamide complexes **QSCM**. The synthesis of the **QSCM** materials is straight and efficient, involving two steps, acylation followed by complexation. The structure of **QSCM** materials was proved by X-ray diffraction on single crystal and by FTIR and NMR spectroscopy. The X-ray spectra prove unambiguously the structure of complexes, e.g for the Zn (II) complex crystallize in the monoclinic P21/n space group type, with a = 1.21602(5) nm, b = 1.55478(5) nm, c = 1.61786(6) nm, α = 90°, β = 106.007(2)°, γ = 90°, V = 2.9402(19) nm^3 and Z = 4. Sulfonamide acts as bidentate ligand trough *Zn-N*quinoline and *Zn-N*sulfonamide bonds, with a tetrahedral coordination environment for Zn^{2+}. The **QSCM** M^{2+} complexes have a good antibacterial activity against gram positive germ *S. aureus* (in the range of 11-21 mm) and gram negative germ *E. coli* (in the range of 12-19 mm). Against fungus *C. albicans* the **QSCM** M^{2+} complexes have an excellent antifungal activity (in the range of 12-25 mm), superior to control Nystatin (18 mm).

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