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Ultrasound assisted synthesis of hybrid quinoline anchored with 4-R-benzenesulfonamide moiety with potential antimicrobial activity

Dumitrela Diaconu [b,d], Violeta Mangalagiu [b], Simona Dunca [c], Dorina Amariucai-Mantu [a,**], Vasilichia Antoci [a], Tiberiu Roman [b], Ionel I. Mangalagiu [a,b,*]

[a] Alexandru Ioan Cuza University of Iasi, Faculty of Chemistry, 11 Carol Bvd, 700506-Iasi, Romania
[b] Alexandru Ioan Cuza University of Iasi, Institute of Interdisciplinary Research – CERNESIM Center, 11 Carol Bvd, 700506-Iasi, Romania
[c] Alexandru Ioan Cuza University of Iasi, Faculty of Biology, 11 Carol Bvd, 700506-Iasi, Romania
[d] Alexandru Ioan Cuza University of Iasi, RECENT-AIR, 11 Carol Bvd, 700506-Iasi, Romania

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ABSTRACT

We present in this paper a direct and efficient study regarding synthesis and spectral characterization of three series of hybrid quinoline anchored with 4-R-benzenesulfonamide moiety, with potential antimicrobial activity, by using ultrasound (US) irradiation and conventional methods (CV). The synthesis pathway is efficient and direct, in two steps: an initial *N*-acylation of 8-amino-quinoline followed by metal complexation with variously M^{2+} metals (Cd^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Pd^{2+}, Zn^{2+}). For both type of reactions, *N*-acylation and complexation, under US irradiations the synthesis have some undeniable advantages: the most relevant being the higher yields, a dramatically decrease for reaction time (with about 150 (one hundred fifty) folds for complexation) comparative with conventional methods (CV) (therefore the spent energy decrease in the same way), a decrease of the amount of used solvents. Taking into account the above considerations these reactions setup could be appreciated as eco-friendly. The structures of the obtained hybrid quinoline – sulfonamide complexes (HQBSM) were determined by elemental analysis and by using spectral investigations: FT-IR, NMR experiments, and X-ray diffraction (in three cases). The FT-IR and NMR spectra of complexes show a similar spectroscopic pattern for all complexes and fully confirm the proposed structures. The X-ray spectra analyses prove without doubts the structure of metal complexes, indicating that their structure depends essentially by two factors: the nature of metal and the nature of sulfonamide-quinoline moieties. Complexes containing 4-methoxy-benzoyl moiety and Zn^{2+} (e.g. **6a**) are tetra-coordinated while in the Ni^{2+} complex (e.g. **6e**) the metallic ion forms a distorted square-based bi-pyramid. In the complexes containing 4-nitro-benzoyl moiety and Cd^{2+} (e.g. **5d**) the metallic ion forms a triangular bipyramid. The antibacterial and antifungal assay reveal that only hybrid **HQBSM** complex (**4e**) (with 4-chloro-phenyl moiety and Ni^{2+} in molecule) have a significant antibacterial activity.

* Corresponding author. Alexandru Ioan Cuza University of Iasi, Faculty of Chemistry, 11 Carol Bvd, 700506-Iasi, Romania.
** Corresponding author.
E-mail addresses: dorina.mantu@uaic.ro (D. Amariucai-Mantu), ionelm@uaic.ro (I.I. Mangalagiu).

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1. Introduction

During the last years, reactions under ultrasound (US) irradiation have turned into a remarkable tool in modern science, especially in medicinal and organic chemistry. Comparative with conventional methods (CV), the exploitation of ultrasound energy in chemical reactions has some significant assets including: higher yields and better product purities, reduced reaction times, the possibility to reach new selectivity and new reactivity, etc. [1–18]. In addition, having lighterr reaction conditions, decreasing amounts of energy, less or suppressed side reactions, using small amounts or no solvents, the reactions become eco-friendly [6,9–13].

Quinoline azaheterocycles and sulfonamide derivatives are priceless scaffolds for both synthetic and pharmacological points of view. Quinoline has been described possessing a large diversity of biological actions such as antiplasmodial, antibacterial and antifungal, *anti*-TB, anticancer, anti-inflammatory, antidepressant, analgesic, anti-Alzheimer's, antihypertensive, etc. [19–30]. The antimicrobial activity of sulfonamide drugs is well known [19,26]. On the other hand, bacterial and fungal deseases represent a serious threaten against human life and, phenomena of drug resistance make the situation even more worse [19,28–30]. In the light of our concerning related to the influence of US irradiation in organic synthesis [12–18] and continuously searching for new biological structures with quinoline and sulfonamide skeleton [21,26,31], we decide to accomplish a detailed study related to the synthesis of new molecules with hybrid quinoline - 4–R-benzenesulfonamide core, by using US irradiation (as nonconventional method) and conventional - room temperature stirring (as conventional method) for synthesis. Another goal was the interest to study the antimicrobial properties of these compounds.

In drug design, a recent and efficient method to obtain more potent antimicrobial derivatives is the molecular hybridization approach, which consist in combining two or more drug pharmacophores *via* a linker resulting in a single chemical entity, usually possesing better biological activity, better pharmacodynamic and pharmacokinetic propierties, lower toxicity and side effects, etc. [20,21]. Metal ions are vital for many biological function and cell process in microorganisms, usually serving as the co-factor for different enzymes [32,33]. Also, the literature describes quinolione - sulfonamide complexes with antimicrobial activity [34–38]. Hence, using molecular hybridization approach it appear logical to combine the quinolione and sulfonamide pharmacophores with a metal, in order to obtain newly hybrid quinoline – benzenesulfonamide - metal (**HQBSM**) derivatives with antimicrobial activity.

2. Experimental details

2.1. Apparatus and analysis

8-aminoquinoline, *p*-(Cl, NO_2, OCH_3)-sulfonyl chlorides and pyridine were purchased from TCI. The solvents were provided from Sigma Aldrich and used in synthesis not dried or degassed. All NMR spectra were acquired with a Bruker Avance III 500 MHz instrument operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The program applyed for data acquisition and processing was TopSpin 3.2 PL5 and the NMR eqquipment is supplied with a 5 mm PABBO detection probe. Chemical shifts were reported in δ units (ppm) relative to the residual peaks of solvents (ref: DMSO –d_6, ^{1}H: 2.50 ppm; ^{13}C: 39.52 ppm). Coupling constants (*J*) were given in Hz. Infrared (IR) data were obtained using a FT-IR VERTEX 70 Bruker spectrophotometer (ATR module: 700–3500 cm^{-1}, spectral resolution 0.4 cm^{-1}, DigiTect detector system). The X-ray structures of the compounds were analyzed by X-ray diffraction on single-crystals, by using a Rigaku Supernova dual Cu/Mo micro-focused source diffractometer. The apparatus is equipped with an EOS - CCD (charge coupled device) detector and a cryo-system (Oxford Cryosystem) allowing to cool down the samples till 80 K (−193.15 °C). A viscous oil-based cryoprotectant (Paratone® N) was used to fix the crystal samples onto the sample holder. The crystals were investigated at a temperature of 293 K using Cu X-ray radiation (CuKα = 1.5418 Å) with a 0.82 Å resolution limit. CrysAlisPro 171.41.110a software from Rigaku OD was employed for data collection, cell refinement and data reduction. Structure determination, visualization and analysis of molecular crystals structure was done in Olex 2 v1.3-ac4 software using ShelXT 2018/2 and ShelXL-2018/3 to solve and refine the proposed structure models of the compounds through direct methods.

The reractions under ultrasounds irradiation was performed by using a Sonics (Sonics VCX-130, USA), with a nominal power of 130 W and a frequency of 20 kHz. The titanium horn (diameter: 6 mm; length: 116 mm) of reactor is fixed to the ultrasonic converter and the titanium probe tip is directly immersed in the reaction mixture. Merck silica gel 60 F^{25}4 plates were used for thin layer

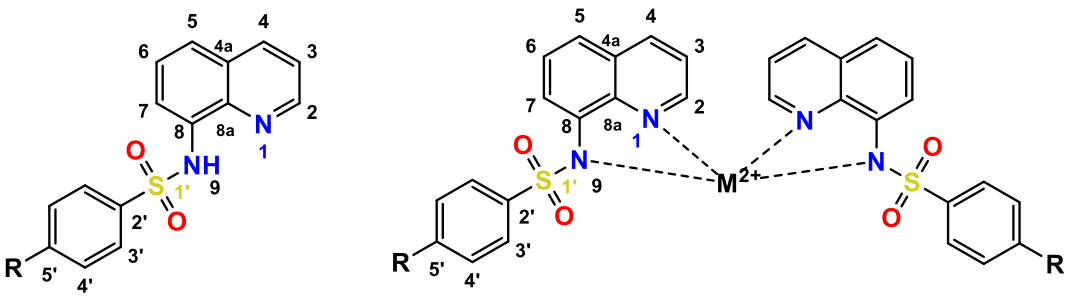


Fig. 1. The number of atoms attributed to ligands and metal complexes.

- *Ligands*

chromatography (TLC) and a UV lamp (λ_{max} = 254 or 365 nm) was used in order to visualize the plates.

The spectral data of compounds **3a**, **3b**, **3c, 4a-d**, **4f**, **5a-c**, **5e**, **6f** are in agreement to the previously reported data [26,36,37], Fig. 1.

2.2. Experimental setup for the synthesis under CV and US irradiation

In order to obtain the desired ligands and their complexes we have used adaptation of previously described procedures in the literature by us [26] or by others researchers [36,37].

2.2.1. Synthesis of the ligands and complexes under conventional methods (CV)

a Synthesis of ligands

8-aminoquinoline (3 mmol) was dissolved in 20 mL CH_2Cl_2 and 2 mL of pyridine was added and cooled on ice bath. Then was added dropwise a solution of 4-chloro/nitro/methoxybenzenesulfonyl chloride (3.3 mmol). The reaction mixture was left to stirred at room temperature for 12 h, than washed with HCl (1 M) and a solution of saturated $NaHCO_3$. The organic layer was dried on Na_2SO_4 and the solvent was extracted in vacuum. The crude solid was purified using column chromatography (CH_2Cl_2/AcOEt = 70/30) giving the corresponding sulfonamide ligand **3a-c**.

b Synthesis of complexes

Zn(II), Cu(II), Co(II), Cd(II), Ni(II) and Pd(II) complexes were prepared from corresponding sulfonamide ligands and metal salts in methanol.

b1 Zn(II), Ni(II) and Pd(II) complexes

Over a methanolic solution (25 mL) of $ZnCl_2$, or $NiCl_2$ x $6H_2O$ or $PdCl_2$ (0.2 mmol), was added under magnetical stirring a mixture of sulfonamide ligand (0.4 mmol) (**3a**, **3b** or **3c**) and 2 mL NH_4OH (solubilized in 40 mL MeOH preliminary). The formed precipitate was separated by filtration. In the case of Zn(II), Ni(II) and Pd(II) complexes in order to deprotonate the sulfonamide nitrogen atom, a base is required to be used.

b2 Cu(II), Co(II) and Cd(II) complexes

To methanolic solution of metal salt $Cu(CH_3COO)_2$x H_2O, $Co(CH_3COO)_2 \times 6H_2O$, respectively $Cd(CH_3COO)_2$ x H_2O (0.2 mmol) in 30 mL MeOH, was added a solution containing 0.4 mmol of sulfonamide ligand (**3a**, **3b**, or **3c**). The solution was left overnight, stirring, and the formed precipitate was separated by filtration.

2.2.2. Synthesis of the ligands and complexes under US irradiation

a Synthesis of ligands

The solution that contains 8-aminoquinoline (3 mmol) and corresponding 4-chloro/nitro/methoxybenzenesulfonyl chloride **2a-c** (3.3 mmol) was introduced in a reaction flask and than irradiated with US. The best reaction conditions were obtained by using a pulse irradiation, 5 s pulse/5 s pause, 50 % from the full power of the generator. After each minute of irradiation TLC was performed. Once reaction is completed, the reaction mixture was processed as indicated for CV.

b Synthesis of complexes

In a tube reaction vessel was placed a methanolic solution (25 mL) of metal salts $ZnCl_2$, $NiCl_2$ x $6H_2O$ or $PdCl_2$, $Cu(CH_3COO)_2$ x H_2O, or $Co(CH_3COO)_2 \times 6H_2O$ or $Cd(CH_3COO)_2$ x H_2O (0.2 mmol) (and 2 mL NH_4OH for chlorides) and sulfonamide ligand (**3a**, **3b**, respectively **3c**) (0.4 mmol). The solution mixture was introduced in a reaction flask and than irradiated with US. The best reaction conditions were obtained by using a pulse irradiation, 5 s pulse/5 s pause, 50 % from the full power of the generator, with an exposure of 6–9 min. Once reaction is completed, the obtained precipitate was separated by filtration.

2.3. Spectral data of synthesized compounds

2.3.1. 4-Nitro-N-(quinolin-8-yl)benzenesulfonamide (**3b**)

White powder; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (1H, t, J = 8.0 Hz, H-6), 7.75 (1H, t, J = 7.5 Hz, H-3), 8.02 (2H, m, H-5, H-7), 8.09 (2H, d, J = 8.5 Hz, 2 *x* H-4'), 8.24 (1H, ad, H-4), 8.24 (2H, d, J = 8.5 Hz, 2 *x* H-4'), 8.77 (1H, ad, J = 3.0 Hz, H-2), 9.37 (1H, s H-9). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 124.84, 126.79, 126.88, 127.78, 128.09, 128.12, 128.48, 129.94, 131.01, 142.70, 144.09, 144.30, 150.07.

2.3.2. 4-Methoxy-N-(quinolin-8-yl)benzenesulfonamide ***(3c)***

White powder; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.72 (3H, s, *p*-OCH_3), 6.98 (2H, d, $J = 8.5$ Hz, 2 *x* H-4′), 7.51 (1H, t, $J = 8.0$ Hz, H-6), 7.58 (1H, t, $J = 7.5$ Hz, H-3), 7.63 (1H, d, $J = 8.0$ Hz, H-5), 7.68 (1H, d, $J = 8.0$ Hz, H-7), 7.85 (2H, d, $J = 8.5$ Hz, 2 *x* H-3'), 8.34 (1H, d, $J = 7.5$ Hz, H-4), 8.86 (1H, ad, $J = 3.0$ Hz, H-2), 9.83 (1H, s H-9). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 124.84, 126.79, 126.88, 127.78, 128.09, 128.12, 128.48, 129.94, 131.01, 142.70, 144.09, 144.30, 150.07.

- *Complexes*

2.3.3. [Ni(N-(quinoline-8-yl)-4-chloro-benzenesulfonamide)2] ***(4e)***

Green cristals; IR (ATR), ν_{max} 1582, 1505, 1470, 1385, 1272, 1131, 1087, 960, 871, 828, 750 cm^{-1}; Anal. Calcd. For $C_{30}H_{20}Cl_2N_4NiO_4S_2$ C, 51.90; H, 2.90; N, 8.45. Found C, 51.80; H, 2.81, N 8.50.

2.3.4. [Pd(N-(quinoline-8-yl)-4-chloro-benzenesulfonamide)2] ***(4f)***

Yellow cristals; IR (ATR), ν_{max} 1576, 1502, 1466, 1381, 1318, 1269, 1191, 1129, 1085, 952, 861, 826, 751 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (4H, d, $J = 8.5$ Hz, 4 *x* H-4′), 7.61 (2H, t, $J = 8.0$ Hz, 2 *x* H-6), 7.66 (2H, d, $J = 8.0$ Hz, 2 *x* H-5), 7.71 (2H, aq, 2 *x* H-3), 7.76 (6H, m, 4 *x* H-3′, 2 *x* H7), 7.82 (4H, d, $J = 8.5$ Hz, 4 *x* H-3'), 8.55 (2H, dd, $J = 1.0$ Hz, $J = 8.0$ Hz, 2 *x* H-4), 9.05 (2H, add, $J = 1.5$ Hz, $J = 5.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 55.42, 113.24, 121.98, 122.51, 124.55, 128.37, 129.05, 133.00, 139.69, 146.37, 146.97, 153.03, 161.32. Anal. Calcd. For $C_{30}H_{20}Cl_2N_4O_4PdS_2$ C, 48.57; H, 2.72; N, 7.55. Found C, 48.60; H, 2.75; N, 7.63.

2.3.5. [Zn(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5a)***

Yellowish cristals; IR (ATR), ν_{max} 1530, 1468, 1350, 1323, 1273, 1193, 1136, 1082, 960, 851, 781, 732 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (2H, m, 2 *x* H-5), 7.45 (4H, m, 2 *x* H-6, 2 *x* H-7), 7.80 (2H, aq, 2 *x* H-3), 8.23 (8H, m, 4 *x* H-3′, 4 *x* H-4'), 8.60 (2H, d, $J = 8.0$ Hz, 2 *x* H-4), 9.22 (2H, ad, $J = 4.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 115.21, 117.96, 122.43, 124.13, 128.28, 128.55, 128.94, 138.30, 140.35, 140.47, 148.43, 148.85, 149.01. Anal. Calcd. For $C_{30}H_{20}N_6O_8S_2$:Zn C, 49.91; H, 2.79; N, 11.64. Found C, 50.02; H, 2.74, N 11.72.

2.3.6. [Cu(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5b)***

Dark brown cristals; IR (ATR), ν_{max} 1523, 1501, 1465, 1380, 1346, 1294, 1144, 1115, 1082, 959, 875, 783, 733 cm^{-1}; Anal. Calcd. For $C_{32}H_{26}CuN_4O_6S_2$ C, 55.68; H, 3.80; N, 8.12. Found C, 55.72; H, 3.85, N 8.04.

2.3.7. [Co(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5c)***

Brickred cristals; IR (ATR), ν_{max} 1528, 1502, 1465, 1383, 1286, 1190, 1190, 1114, 1086, 957, 849, 786, 733 cm^{-1}; Anal. Calcd. For $C_{30}H_{20}CoN_6O_8S_2$ C, 50.36; H, 2.82; N, 11.74. Found C, 50.39; H, 2.78, N 11.79.

2.3.8. [Cd(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5d)***

Yellow cristals; IR (ATR), ν_{max} 1527, 1468, 1351, 1320, 1269, 1186, 1123, 1069, 960, 823, 779, 757 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (6H, m, 2 *x* H-5, 2 *x* H-6, 2 *x* H-7), 7.71 (2H, aq, 2 *x* H-3), 8.13 (4H, d, $J = 8.5$ Hz, 4 *x* H-3′), 8.13 (4H, d, $J = 8.5$ Hz, 4 *x* H-4'), 8.43 (2H, d, $J = 8.0$ Hz, 2 *x* H-4), 9.17 (2H, ad, $J = 4.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 114.70, 117.28, 121.80, 123.55, 127.56, 128.80, 129.12, 138.46, 138.65, 141.00, 148.54, 148.76, 149.63. Anal. Calcd. For $C_{30}H_{20}N_6NiO_8S_2$ C, 50.37; H, 2.82; N, 11.75. Found C, 50.31; H, 2.86, N 11.68.

2.3.9. [Ni(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5e)***

Green cristals; IR (ATR), ν_{max} 1524, 1466, 1350, 1319, 1268, 1185, 1112, 958, 848, 822, 777, 735 cm^{-1}; Anal. Calcd. For $C_{30}H_{20}N_6NiO_8S_2$ C, 50.37; H, 2.82; N, 11.75. Found C, 50.41; H, 2.78, N 11.80.

2.3.10. [Pd(N-(quinoline-8-yl)-4-nitro-benzenesulfonamide)2] ***(5f)***

Yellow cristals; IR (ATR), ν_{max} 1524, 1350, 1300, 1149, 851, 796, 737 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (6H, m, 2 *x* H-5, 2 *x* H-6, 2 *x* H-7), 7.72 (2H, aq, 2 *x* H-3), 7.70 (2H, dd, $J = 1.0$ Hz, $J = 7.0$ Hz, 2 *x* H-5), 7.82 (4H, d, $J = 8.5$ Hz, 4 *x* H-3′), 8.14 (4H, d, $J = 8.5$ Hz, 4 *x* H-3′), 8.30 (2H, d, $J = 8.5$ Hz, 2 *x* H-4'), 8.37 (2H, d, $J = 8.0$ Hz, 2 *x* H-4), 8.81 (2H, add, $J = 1.5$ Hz, $J = 5.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 114.75, 117.32, 121.79, 123.51, 127.69, 128.75, 129.10, 138.45, 138.67, 141.05, 148.96, 148.23, 149.05. Anal. Calcd. For $C_{30}H_{20}N_6O_8PdS_2$ C, 47.22; H, 2.64; N, 11.01. Found C, 47.25; H, 2.68; N, 10.95.

2.3.11. [Zn(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6a)***

Yellowish cristals; IR (ATR), ν_{max} 1599, 1504, 1392, 1325, 1261, 1194, 1149, 1089, 978, 876, 792, 758 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.76 (6H, s, 2 *x* *p*-OCH_3), 6.96 (4H, d, $J = 9$ Hz, 4 *x* H-4′), 7.37 (2H, m, 2 *x* H-7), 7.53 (4H, m, 2 *x* H-5, 2 *x* H-6), 7.81 (2H, aq, 2 *x* H-3), 7.98 (4H, d, $J = 9$ Hz, 4 *x* H-3'), 8.70 (2H, dd, $J = 1.5$ Hz, $J = 8.5$ Hz, 2 *x* H-4), 8.94 (2H, add, $J = 1$ Hz, $J = 4.5$ Hz, 2 *x* H-2).^{13}C NMR, (125 MHz, DMSO-d_6) δ 55.49, 113.99, 114.36, 117.64, 122.71, 128.61, 128.85, 129.27, 133.58, 138.12, 140.36, 140.85, 148.89, 161.66. Anal. Calcd. For $C_{32}H_{26}N_4O_6S_2Zn$ C, 55.54; H, 3.79; N, 8.10. Found C, 55.44; H, 3.84, N 8.04.

2.3.12. [Cu(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6b)***

Dark brown cristals; IR (ATR), ν_{max}1580, 1501, 1380, 1321, 1263, 1286, 1163, 1086, 962, 871, 799 cm^{-1}; Anal. Calcd. For

$C_{32}H_{26}CuN_4O_6S_2$ C, 55.68; H, 3.80; N, 8.12. Found C, 55.72; H, 3.85, N 8.04.

2.3.13. [Co(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6c)***

Brickred cristals; IR (ATR), ν_{max}1601, 1503, 1385, 1291, 1262, 1157, 1088, 1028, 956, 866, 757 cm^{-1}; Anal. Calcd. For $C_{32}H_{26}CoN_4O_6S_2$ C, 56.06; H, 3.82; N, 8.17. Found C, 56.11; H, 3.75, N 8.10.

2.3.14. [Cd(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6d)***

White cristals; IR (ATR), ν_{max} 1604, 1500, 1470, 1393, 1324, 1284, 1252, 1137, 1076, 960, 858, 824, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.73 (6H, s, 2 *x p*-OCH_3), 6.86 (4H, d, $J = 8.5$ Hz, 4 *x* H-4′), 7.37 (6H, m, 2 *x* H-7, 2 *x* H-5, 2 *x* H-6), 7.65 (2H, aq, 2 *x* H-3), 7.94 (4H, d, $J = 9$ Hz, 4 *x* H-3'), 8.37 (2H, d, $J = 8.0$ Hz, 2 *x* H-4), 9.14 (2H, ad, $J = 4.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 55.27, 113.28, 114.34, 115.97, 121.46, 127.51, 128.97, 129.39, 135.50, 138.32, 138.49, 141.88, 148.32, 160.81. Anal. Calcd. For $C_{32}H_{26}CdN_4O_6S_2$ C, 52.00; H, 3.55; N, 7.58. Found C, 52.10; H, 3.78, N 7.60.

2.3.15. [Ni(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6e)***

Green cristals; IR (ATR), ν_{max} 1598, 1505, 1465, 1386, 1322, 1246, 1129, 1082, 946, 865, 766 cm^{-1}; Anal. Calcd. For $C_{32}H_{26}N_4NiO_6S_2$ C, 56.08; H, 3.82; N, 8.17. Found C, 56.00; H, 3.90, N 8.10.

2.3.16. [Pd(N-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)2] ***(6f)***

Yellowish cristals; IR (ATR), ν_{max} 1596, 1499, 1317, 1259, 1146, 1089, 1025, 936, 847, 791, 777 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.34 (6H, s, 2 *x p*-OCH_3), 6.69 (4H, d, $J = 8.5$ Hz, 4 *x* H-4′), 7.58 (4H, m, 2 *x* H-6, 2 *x* H-7), 7.69 (2H, aq, 2 *x* H-3), 7.70 (2H, dd, $J = 1.0$ Hz, $J = 7.0$ Hz, 2 *x* H-5), 7.82 (4H, d, $J = 8.5$ Hz, 4 *x* H-3'), 8.55 (2H, dd, $J = 1.0$ Hz, $J = 8.0$ Hz, 2 *x* H-4), 9.05 (2H, add, $J = 1.5$ Hz, $J = 5.5$ Hz, 2 *x* H-2). ^{13}C NMR, (125 MHz, DMSO-d_6) δ 55.42, 113.24, 121.98, 122.51, 124.55, 128.37, 129.05, 133.00, 139.69, 146.37, 146.97, 153.03, 161.32. Anal. Calcd. For $C_{32}H_{26}N_4O_6PdS_2$ C, 52.43; H, 3.57; N, 7.64. Found C, 52.51; H, 3.62; N, 7.54.

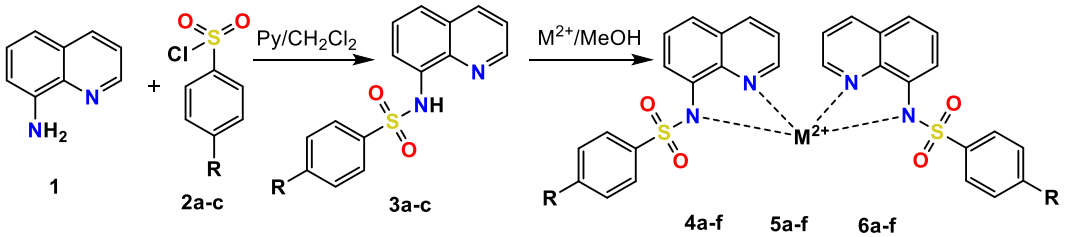
2.4. Antimicrobial assay

A Disk-diffusion method

The *in vitro* antibacterial and antifungal activity of the newly **HQBSM** derivatives were settled by using the Kirby-Bauer disk-diffusion assay. The assay is using Müeller Hinton agar medium for antibacterial determinations and Sabouraud nutrient agar medium for antifungal determinations. The *in vitro* antibacterial activity was rated against diffrent bacterial strains (Gram-positive strain *Staphylococcus aureus ATCC 25923*, Gram-negative strain *Escherichia coli ATCC 25922*) while the antifungal activity was rated against *Candida albicans ATCC 1023123*. For bacterial tests (*S. aureus* and *E. coli*), the positive control (C+) used was Gentamicin, while for fungal assay Nystatin was used. Sterile filter paper disks inoculated with DMSO 3 % was used as negative control (*C*-).

B Broth microdilution assay. The minimum inhibitory concentration (MIC)

The MIC were determined by broth microdilution assay, by using the 96-well microtiter plate (microdilution) technique. The MIC was rated against diffrent bacterial strains (Gram-positive strain *Staphylococcus aureus ATCC 25923*, Gram-negative strain *Escherichia coli ATCC 25922*) while the antifungal activity was rated against *Candida albicans ATCC 1023123*. For each tested microbial strain, were used a positive control C+ (containing 80 μL of MH growth medium and 10 μL of antimicrobial compound) and a negative control *C*- (containing 80 μL of MH growth medium and 10 μL of diluted microbial culture). Resazurin (redox dye) was used as colorimetric



	a (Zn^{2+})	b (Cu^{2+})	c (Co^{2+})	d (Cd^{2+})	e (Ni^{2+})	f (Pd^{2+})
4 (R= -Cl)	4a	4b	4c	4d	4e	4f
5 (R= -NO_2)	5a	5b	5c	5d	5e	5f
6 (R= -OCH_3)	6a	6b	6c	6d	6e	6f

Scheme 1. Reaction scheme for obtaining hybrid metal quinoline – 4-R-benzenesulfonamide derivatives.

indicator.

A complete description of this technique is presented in the Supporting information file.

3. Results and discussion

3.1. Chemistry and spectral characterization

In a preliminary communication in this journal [26] we presented a general procedure to obtain quinoline – sulfonamide - metal derivatives. Using an analogus setup, we obtained three series of HQBSM hybrids, each series having as substituent –R in the 4-th position of sulphone amide moiety a chlorine atom (**4a-f**), a nitro (**5a-f**) or a methoxy group (**6a-f**). The synthesis took place in two steps: acylation of 8-aminoquinoline with 4-chloro/nitro/methoxy-benzenesulfonyl chlorides, followed in the second step by complexation of ligands (**3a-c**, namely quinoline – 4-R-benzenesulfonamide) with metal acetate (Cu^{2+}, Co^{2+}, Cd^{2+}) or chloride (Zn^{2+}, Ni^{2+}, Pd^{2+}), when the desired compounds **HQBSM 4a-f, 5a-f and 6a-f** are obtained, Scheme 1. The obtained hybrid compounds (sulfonamide ligands and complexes) are stable both in the solid state and in the solution. Also, complexes with divalent metals made by synthesis are air-stable. Ligands are soluble in dichloromethane (DCM) or chloroform ($CHCl_3$), while complexes are slightly soluble in chloroform ($CHCl_3$) and dimethyl sulfoxide (DMSO).

Under conventional methods (CV), both the *N*-acylation and complexation reactions, have some substantial drawbacks, the most importantat being the long reaction time (240 min for *N*-acylation respectively 720 min for complexation), moderate to good yields (around 50–85 %) and high amounts of used solvents. In order to withdraw these drawbacks, we decide to perform these reactions by using US irradiation. The obtained results are rationalized in Table 1. Analysing the data from Table 1 reveal that under US irradiation the experimental setup have some undeniable advantages: a substantially decreasing of reaction time (from 240 min to 4 min for *N*-acylation, respectively from 720 min to 6–9 min for complexation), a remarkable acceleration of reaction and a considerable decrease of the consumed energy, an increased yields (with about 10–15 %), and a decreasing of the amount of used solvents. Consequently, this reaction setup procedure could be considered as eco-friendly.

3.1.1. FT-IR studies

In the FT-IR spectra of quinoline – 4-R-benzenesulfonamide ligand **3c** and its complexes with divalent ions **6a-f** the most relevant signals are those one of N–H group, SO_2 group, *S*–N group and *C*–N group (See Supporting Informations- Fig. S1). In Table 2, are indicated the assignements of the most important streching vibration bands.

In the FT-IR spectrum of ligand **3c**, the band from 3281 cm^{-1} (medium intensity), was assigned to the N–H stretching vibration from sulfonamide group. For complexes **6a-f**, the absence of this band in their corresponding FT-IR spectra represent a stronf evidence for the fact that deprotonation of the nitrogen atom from the sulfonamide has occurred and its coordination with the metal ion took place. The absorptions bands of SO_2 group appear at very different wave numbers in the FT-IR spectra for ligand **3c** and complexes **6a-f**. For the ligand **3c** the asymmetric stretching vibration of sulfonyl group appear at 1368 cm^{-1} while in spectra of complexes **6a-f** are shifted with approximate 20 cm^{-1} upwards; analogous, the band corresponding to the symmetric stretching vibration of the SO_2 group are shifted with approximate 20 cm^{-1} downwards in complexes comparative with the ligand (in which appear at 1165 cm^{-1}). The most probable, these differences could be explained because in the free ligand a larger double bond character of the S═O bonds could be incriminated and also because of the different spatial orientation of S═O bonds in complexes **6a-f**. The *S*–N stretching vibration bands in the spectra of the complexes it is also shifted with approximate 40 cm^{-1} upwards, hence proving the donor role of the nitrogen atom in relation with the metal atom.

Table 1
Experimental setup for *N*-acylation and complexation reactions under conventional methods (CV) and ultrasound irradiation (US).

		Sulfonamide ligands 2a-c						Complexes 4a-f					
		2a	2 b	2c				4a	4 b	4c	4 d	4e	4f
Reaction time (min)	CV	240	240	240				720	720	720	720	720	720
	US[a]	4	4	4				6	6	6	6	6	9
Yield (%)	CV	88	80	82				58	39	42	64	38	45
	US[a]	96	85	90				80	76	62	72	60	67
		Complexes 5a-f						**Complexes 6a-f**					
		5a	**5b**	**5c**	**5d**	**5e**	**5f**	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**
Reaction time (min)	CV	720	720	720	720	720	720	720	720	720	720	720	720
	US[b]	6	6	6	6	6	9	6	6	6	6	6	9
Yield (%)	CV	58	44	38	48	48	36	70	52	48	72	46	48
	US[b]	74	67	70	62	75	44	82	76	70	88	72	70

a: 50 % from the full power of the generator (A = 50 %); b: 100 % from the full power of the generator (A = 100 %).

The structure of the obtained hybrids was confirmed by elemental and spectral analysis. The infrared spectroscopy (FT-IR), NMR spectroscopy (^1H NMR, ^{13}C NMR, 2D-COSY, 2D-HMQC, 2D-HMBC), and X-ray spectroscopy on monocrystal confirm the structure of the **HQBSM** hybrids. Thus, in the case of M^{2+} [*N*-(quinolin-8-yl)-4-methoxy-benzenesulfonamide] hybrid class HQBSM **6a-f**, considered as representative for the series of hybrids, the spectral analysis demonstrate the following data presented bellow.

Table 2
Relevant streching vibration bands of quinoline – 4-R-benzenesulfonamide ligand **3c** (R = –OCH_3) and its complexes with divalent ions **6a-f**.

ν (cm^{-1})	ν_{N-H}	ν_{asSO2}	ν_{symSO2}	ν_{C-N}	ν_{S-N}
Sulfonamide ligand **(3c)**	3281(m)	1368 (*s*-m)	1165(s)	1504(m)	922(m)
Zn complex **(6a)**	–	1385 (*s*-m)	1149(s)	1503(m)	978(m)
Cu complex **(6b)**	–	1380 (*s*-m)	1143(s)	1501(s)	962(m)
Co complex **(6c)**	–	1385 (*s*-m)	1157(m)	1503(m)	956(m)
Cd complex **(6d)**	–	1393 (*s*-m)	1135(m)	1500(m)	960(m)
Ni complex **(6e)**	–	1387 (*s*-m)	1129(m)	1505(m)	946(m)
Pd complex **(6f)**	–	1318 (*s*-m)	1146(m)	1499(m)	936(m)

ν—stretching; s—strong; m—medium; w—weak; as—asymmetric; *sym*—symmetric.

3.1.2. NMR studies

In the ^{1}H NMR spectra of the ligand 4-methoxybenzenesulfonamide **3c** and its complexes **6a-f** (See Supporting Information-Fig. S2), the most relevant signals are those one of the hydrogen atoms **H_9**, **H_2**, **H_3**, **H_4** (in Table 3 are indicated the assignements of hydrogens). The most of particular interest signal in the ^{1}H NMR spectra, is those one corresponding to the hydrogen atom from sulfonamide group **H_9**, which appear in ligand to a chemical shift of 9.83 ppm while in complexes spectra is absent; this is a solid proof of coordination with the metal ion. Furthermore we observe in the ^{1}H NMR spectra of complexes **6a-f** that there is a slightly shift towards down field values of the signals for the hydrogen atoms that are closely to the metal ion, **H_2**, **H_3**, **H_4** (from pyridine ring), as a result of electron density transfer from the ligand to the metal ion.

In the ^{13}C NMR spectra of the ligand **3c** and its complexes **6a-f**, the most relevant signals are attributed to the carbon atoms **C_2'**, **C_8**, **C_5** and **C_7** (in Table 4 are indicated the assignements of carbons). In the spectra of complexes **6a-f**, the **C_2'** and **C_8** carbons appear to a chemical shift of about 134 ppm for C_2', respectively 141 ppm for **C_8**, higher with about 4 ppm for **C_2'**, respectively, with about 8 ppm for **C_8**, comparative with the free ligand **3c**. The **C_2'** carbons (*ipso*- SO_2 group from sulfonamide, carbon from benzene-sulfonyl) and **C_8** carbons (*ipso*- N atom from sulfonamide group, carbon from attached benzene ring of quinoline) appear to so high chemical shifts, due to the powerful deshielding efect of sulfonamide group and the metal ion (see Table 5).

The **C_5** and **C_7** carbons are the most shielded (they appear to a chemical shift of about 117 ppm for **C_5**, respectively 115 ppm for **C_7**), downfield with about 5 ppm for **C_5**, respectively, with about 2 ppm for **C_7**, comparative with the free ligand **3c**. The most reasonable explication for these behaviour, is the ecranation effect exerted by the benzene electronic cloud from vicinity (benzene from sulfonamide moiety), as it could be seen in the X-ray structure bellow.

3.1.2.1. X-ray monocrystal studies. In the case of compounds **6a**, **6e** and **5d** (from M^{2+}[*N*-(quinolin-8-yl)-4-nitro-benzenesulfonamide] hybrid class HQBSM **5a-f)** the structure of complexes was proven without ambiguity by single-crystal X-ray analysis (compounds **6b**, **6c**, **6d** and **6f** do not have proper crystals), Figs. 2–4.

In the case of compound **6a** the Zn atom is tetra-coordinated by two sulfonamide-quinoline moieties (Figs. 2 and 5-b) by four atoms where two are represented by N (quinoline-type) and the rest of two by N (sulfonamide-type) atoms. The molecule of the complex is formed by two asymmetric units where the centre corresponds to the position of Zn atom. As the molecule is symmetric, the bond lengths of the coordinating atoms can be described only as Zn1–N1 (quinolinic) with a length of 2.063 Å and Zn1–N2 (sulfonamide) with 1.964 Å. Comparative with the obtained results in our previous work in analogous cases [26], some similarities are found in the bond lengths values of $M-$ N (sulfonamide-type), where M are represented by tetra-coordinated Co^{2+} and Cu^{2+} ions, with values ranging from 1.970 Å to 1.983 Å for Co atoms and 1.944 Å to 1.960 Å for Cu atoms. The noticeable differences are present at the $M-$ N (quinoline) bonds where the length is reported in the range of 1.980 Å till 2.038 Å, whereas in the present study the Zn–N (quinolinic) bond length is 2.063 Å. The most reasonable explanation of the bonds lengthening is represented by the absence of Jahn–Teller distortions effect in case of Zn–N (quinolinic) bond as the same phenomena was reported by *Samuel Tetteh* for the tetra-coordinated Zn^{2+} ions with 1-Methylimidazole Complexes [39].

In the complex **6e**, the Ni atom is coordinated by two sulfonamide-quinoline moieties, one molecule of water (W) and one molecule of methanol (M). The atoms arrangement around the Ni metallic ion in the case of complex **6e**, forms a distorted square-based bi-pyramid (Figs. 3 and 5-a), having in the top of one pyramid a nitrogen atom (the N (quinoline-type)) and an oxigen atom (the O (water)) in the other pyramid. This type of arrangement does not favor the formation of perfect square-based pyramid as the angle between OW99–Ni1–N3 (quinolinic) is 175.93° with bond lengths of 2.127 Å for OW99–Ni1 and 2.060 Å for Ni1–N3. The base of the coordination system is represented by Ni as the central placed atom, bonded with 4 atoms where 2 are represented by N (sulfonamide-type) atoms, one by the remaining N (quinoline-type) atom and another one with the O atom provided by the methanol molecule. The

Table 3
Relevant signals from ^{1}H NMR spectra of quinoline – 4-R-benzenesulfonamide ligand **3c** and its complexes with divalent ions **6a**, **6d** and **6f**.

Compound/Proton	H9	H2	H3	H4
3c	9.83	8.85	7.57	8.34
6a	–	8.95	7.81	8.70
6d	–	9.15	7.65	8.37
6f	–	9.05	7.70	8.55

Table 4
Relevant signals from ^{13}C NMR spectra of quinoline – 4-R-benzenesulfonamide ligand **3c** and its complexes with divalent ions **6a**, **6d** and **6f**.

Compound/Carbon	C2′	C8	C5	C7
3c	130.83	133.67	122.75	116.09
6a	133.58	141.36	117.64	114.36
6d	135.50	141.88	116.97	115.34
6f	139.69	146.37	122.51	121.98

Table 5
Crystal data and structure refinement parameters for the complexes **6a**, **6e** and **5d**.

Compound	6a	6e	5 d
Empirical formula	$C_{32}H_{26}ZnN_4O_6S_2$	$C_{33}H_{32}NiN_4O_8S_2xCH_3OH$	$C_{30}H_{22}CdN_6O_9S_2$
Formula weight	692.06	767.50	787.05
Temperature/K	293 (2)	293 (2)	293 (2)
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	*C*2/*c*	$P2_12_12_1$	$P12_1/c1$
a/Å	14.18884 (16)	10.3496 (2)	28.8176 (4)
b/Å	17.30883 (16)	13.7000 (3)	11.1632 (2)
c/Å	13.79318 (19)	24.2832 (4)	9.69690 (10)
α/°	90	90	90
β/°	111.3429 (15)	90	90.1500 (10)
γ/°	90	90	90
Volume/Å^3	3155.18 (7)	3443.10 (12)	3119.45 (8)
Z	4	4	4
ρ_{calc}g/cm^3	1.457	1.481	1.676
μ/mm^{-1}	2.743	2.464	7.388
F(000)	1424.0	1600.0	1584.0
Crystal size/mm^3	0.19 × 0.19 × 0.64	0.12 × 0.13 × 0.91	0.54 × 0.06 × 0.05
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	3.4370 to 70.9180	3.700 to 71.186	3.0670 to 70.7692
Index ranges	−17 ≤ h ≤ 17, −20 ≤ k ≤ 21, −14 ≤ l ≤ 16	−12 ≤ h ≤ 9, −16 ≤ k ≤ 16, −29 ≤ l ≤ 29	−35 ≤ h ≤ 34, −13 ≤ k ≤ 10, −11 ≤ l ≤ 10
Reflections collected	14,783	18,116	19,572
Independent reflections	3017 [R_{int} = 0.0171, R_{sigma} = 0.0102]	6322 [R_{int} = 0.0190, R_{sigma} = 0.0185]	5552 [R_{int} = 0.0213, R_{sigma} = 0.0217]
Data/restraints/ parameters	3017/0/205	6322/12/449	5552/1/436
Goodness-of-fit on F^2	1.048	1.081	1.019
Final R indexes [I > = 2σ (I)]	R_1 = 0.0266, wR_2 = 0.0759	R_1 = 0.0365, wR_2 = 0.1083	R_1 = 0.0259, wR_2 = 0.0663
Final R indexes [all data]	R_1 = 0.0271, wR_2 = 0.0763	R_1 = 0.0373, wR_2 = 0.1073	R_1 = 0.0337, wR_2 = 0.0717
Largest diff. Peak/hole/e Å^{-3}	0.212/-0.352	0.590/-0.373	0.225/-0.379
Flack	–	0.348 (5)	–

Antimicrobial assay.

bonds length of Ni with the N2 (sulfonamide-type) atom is 2.133 Å, the second one Ni1–N4 is 2.124 Å slightly larger than Ni1–N1 (quinoline) – 2.052 Å and Ni1–N3 - 2.060 Å.

In the complex **5d**, the Cd atom is coordinated by two sulfonamide-quinoline moieties and one molecule of water. In compound **5d**, the geometry of Cd atom resembles with a triangular bipyramid (Figs. 4 and 5-c). Beside the oxygen atom from the coordinated water molecule, cadmium atom bonds bidentate with two sulfonamido-quinoline moieties as follow: Cd–N1 (quinolinic) with a length of 2.317 Å, Cd–N2 (sulfonamide) with 2.251 Å and Cd–N4 (quinolinic) with a length of 2.317 Å, Cd–N5 (sulfonamide) with 2.261 Å respectively.

Asymmetric unit (A.U.) of complex ([4-metoxy-*N*-(quinoline-8-yl) benzenesulfonamidato-κ^{2}N,N']zinc(II)) can be represented as half of the molecule due to its centrosymmetric arrangement (described by the *-x,y,1/2-z* symmetry code) as shown in Fig. 6. This complex crystallises in a monoclinic system with *C*2/*c*, a = 14.1888 Å, b = 17.3088 Å, c = 13.7932 Å, $\alpha = \gamma = 90.0^\circ$, $\beta = 111.343^\circ$ space group, occupying a total volume of 3155.18 Å^3 specific for a number of 4 molecules (see Supplementary information – Fig. S3).

This solvent-free compound does not form in the packing structure any typical inter-molecular H-bonds, instead it is stabilised by a zig-zag net-like arrangement of molecules as Fig. 6-A suggests.

In the asymmetric unit (A.U.) of complex **6e** the structure contain a Ni^{2+} cation coordinated by two molecules of sulfonamido-quinoline derivatives (4-metoxy-*N*-(quinoline-8-yl) benzenesulfonamide) through both N atoms from the quinolinic core, one molecule of methanol (M) and one molecule of water (W). Beside the above menitioned moities, the asymmetric unit contain and a molecule of methanol as solvent (S), Fig. S5 (from Supporting information). The compound crystallises in an orthorhombic arrangement with $P2_12_12_1$, a = 10.349 Å, b = 13.700 Å, c = 24.283 Å, $\alpha = \beta = \gamma = 90^\circ$ space group, occupying a total volume of 3443.10 Å^3 specific for 4

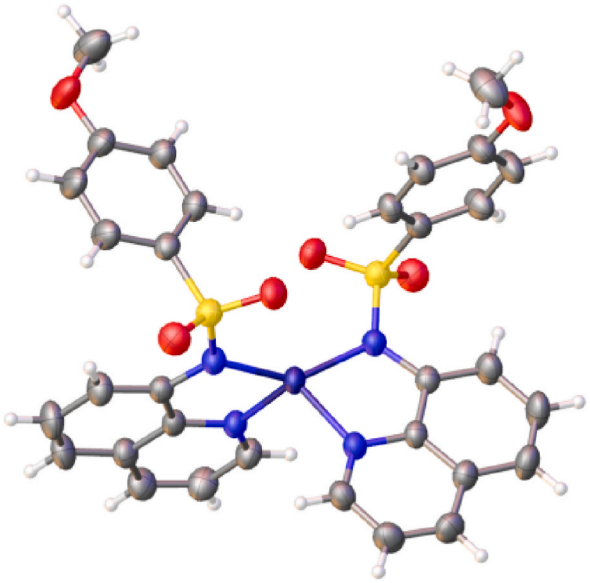


Fig. 2. Molecular structure of [Zn(*N*-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)$_2$] **6a** complex.

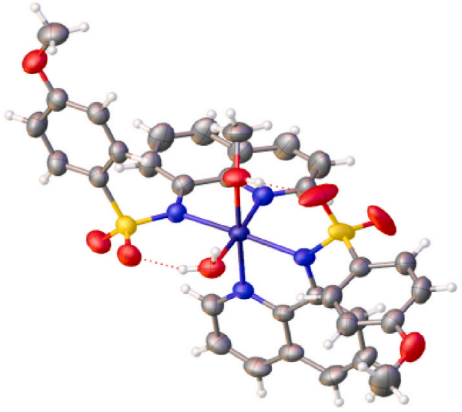


Fig. 3. Molecular structure of [Ni(*N*-(quinoline-8-yl)-4-methoxy-benzenesulfonamide)$_2$] **6e** complex.

A U. In-between each 2 of A.U. there are found 3 intermolecular H-bonds: O99W–H99A···O4 with a length of 1.88 Å, O99W–H99B···O5 with a length of 2.09 Å and O99M-H99 M···O1 with a length of 1.82 Å that help stabilize the complex arrangement as depicted in Fig. S5 (from Supporting information).

The 2 × 2 × 2 packing structure of complex **6e** (Fig. 6-B), reveals a tight array between the complex **6e** molecules with the methanol solvent molecules (which are occupying the free spaces in the packing crystals).

Asymmetric unit of complex **5d** contains two molecules of sulfonamido-quinoline (4-metoxy-*N*-(quinoline-8-yl) benzenesulfonamide bonded through both N atoms to Cd atom, Fig. S6 (from Supporting information). To fulfil the coordination sphere of cadmium, one water (W) molecule is bonded to the central atom, at a specific distance of 2.23 Å. Even the structure of complex contains a water molecule, this structure can be considered solvent free as far as the crystal does not contain any free water solvent (S) in its crystal system packing. The complex molecules crystallise in a monoclinic arrangement with $P12_1/c1$ a = 28.8176 (4) Å, b = 11.1632 (2) Å, c = 9.69690 (10) Å, $\alpha = \gamma = 90.0^{\circ}$, $\beta = 90.15^{\circ}$ space group, occupying a total volume of 3119.45 (8) Å^3 specific for a number of 4 molecules. Each molecule of Cd^{2+} complex interacts with other two by intermolecular H-bond *via* coordinated water (W), as it is shown in Fig. S6 (from Supporting information). Both hydrogen atoms from the coordinated water molecule interract as follow: O1W–H1WA···O1 at a distance of 1.87 Å and O1W–H1WB···O5 at a distance of 1.90 Å, stabilising its structure.

The 2 × 2 × 2 packing structure of complex **5d** presented in Fig. 6-C, reveals a compact parallel-layered arrangement.

The antimicrobial (antibacterial and antifungal) activities of the hybrids **HQBSM** derivatives were evaluated by the disk diffusion Kirby-Bauer method [29,30,38]. For the assay we used *Staphylococcus aureus ATCC 25923* (as Gram-positive bacteria), *Escherichia coli ATCC 25922* (as Gram-negative bacteria) and fungus *Candida albicans ATCC 10231*. The positive control (C+) for *S. aureus* and *E. coli*

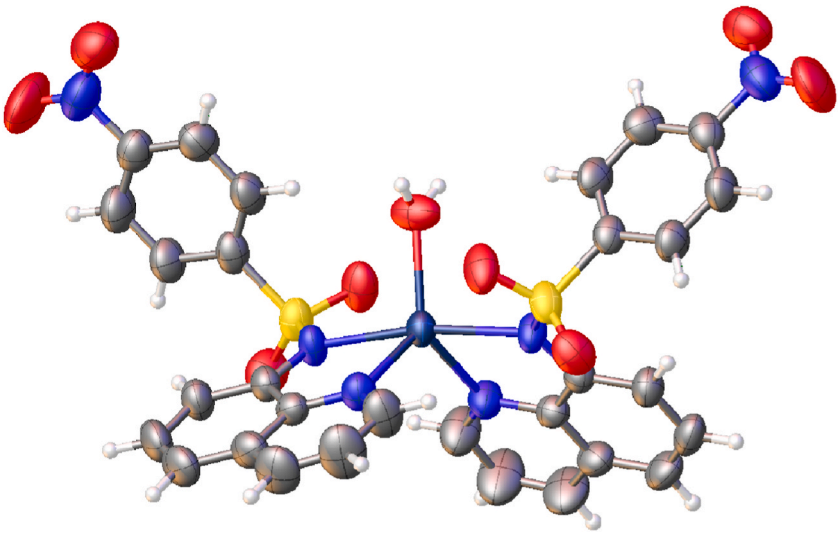


Fig. 4. Molecular structure of [Cd(*N*-(quinoline-8-yl)-4-nitro-benzenesulfonamide)$_2$] **5d** complex.

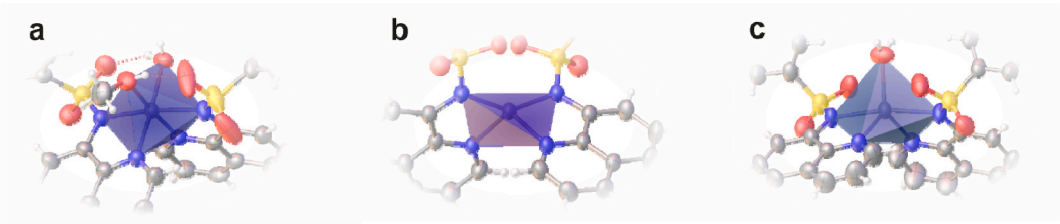


Fig. 5. The coordination of central atoms in complexes. a. **6e**, $C_{33}H_{32}NiN_4O_8S_2$ x CH_3OH; b. **6a**, $C_{32}H_{26}ZnN_4O_6S_2$; c. **5d**, $C_{30}H_{22}CdN_6O_9S_2$. Representation of individual polyhedra accordingly to the complex molecules.

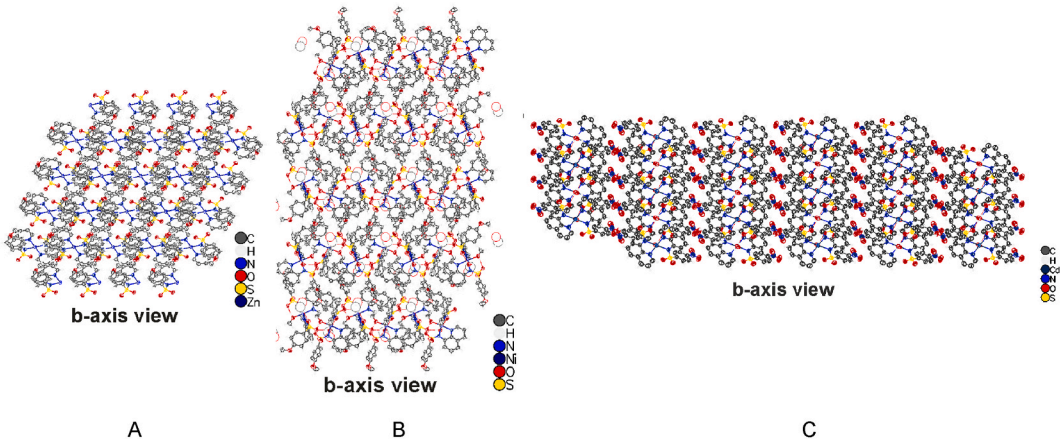


Fig. 6. 2 × 2 × 2 packing structure of the complexes (A-**6a**, B-**6e** and C-**5d**).
*Hydrogen atoms are not highlighted.

was Gentamicin while for *C. albicans* the positive control was Nystatin. In all cases as negative control (*C*-) we used sterile filter paper disks seeded with DMSO 3 %. The accomlished results are indicated as diameters of inhibition zones (mm) and, for ligands **3b** and **3c** and their complexes **(5a-f)**, respectively **(6a-f)**, are presented in Tabel 6. The hybrid compounds **4e** and **4f** are part of the series of complexes that have as a ligand 4-chlorobenzenesulfonamide **3a**.

The data from Table 6 reveal that only one of the tested compounds, [Ni(*N*-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$], **(4e)**, has activity, being active against the bacterial strain *S. aureus*, with a diameter of inhibition zone of 11 mm.

The antimicrobial evaluation continued with the evaluation of the minimum inhibitory concentration (MIC) of the hybrids using the standardized broth microdilution assay method [39], the obtained results being presented in Table 7. The MIC represent the lowest concentration of the tested compound which stop visible growth of the tested microorganism.

Having in view the above results we may conclude that the factor that has a significant influence for antibacterial and antifungal activity is the presence of 4-chloro-benzoyl moiety into the hybrid structure; the presence of either a nitro or methoxy group at 4-position of the phenyl moiety as in **3b**, **3c** and complexes **5a-f**, respectively **6a-f** induced total loss of activity. Simmilar results were obatined by other researchers in analogous cases [29,30].

4. Conclusions

In this paper we reported a clear and efficient study related to synthesis and spectral characterization of three series of quinoline hybrids anchored with 4-R-benzenesulfonamide moiety, with potential antimicrobial activity, by using ultrasound irradiation and conventional methods. The synthesis pathway is direct, in two steps, involving an *N*-acylation reaction of amino-qunoline followed by metal complexation with variously M^{2+} metals (Cd^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Pd^{2+}, Zn^{2+}). Under US irradiations the synthesis have some undeniable advantages, the most relevant being the higher yields and better product purities, a dramatically decrease for reaction time (with about 150 (one hundered fifty) folds for complexation) comparative with conventional methods (CV) (hence the consumed energy decrease in the same way), a substantial decrease of the amount of used solvents. Taking into account the above considerations these reactions setup could be considered as environmentally friendly. The **HQBSM** complexes were characterised by IR and NMR spectroscopy, elemental analysis and X-ray crystallography (three cases). The FT-IR and NMR spectra of complexes show a similar spectroscopic pattern for all complexes and fully confirm the proposed structures. The X-ray spectra reveal that the structure of complexes depend essentially by two factors: the nature of metal and the nature of sulfonamide-quinoline moieties. In the Zn^{2+} complexes (e.g **6a**) the metal is tetra-coordinated by two sulfonamide-quinoline moieties. The Zn–N (quinolinic) bond length is 2.063 Å, higher than usual, due to the absence of Jahn–Teller distortions effect in case of Zn–N (quinolinic) bond. In the Ni^{2+} complexes (e.g **6e**) the metal form a distorted square-based bi-pyramid, being coordinated by two sulfonamide-quinoline moieties, one molecule of water (W) and one molecule of methanol (M). In case of the Cd^{2+} complexes (e.g **5d**), the Cd atom form a triangular bipyramid, being coordinated by two sulfonamide-quinoline moieties and one molecule of water. In the packing crystals, the complexes **5** and **6** have different networks, again, according with the nature of metal and sulfonamide-quinoline moieties. The Zn^{2+} complexes (e.g **6a**) have an asymmetric unit (A.U.) that can be represented as half of the molecule due to its centrosymmetric arrangement and, the packing structure is stabilised by a zig-zag net-like arrangement of molecules. The Ni^{2+} complexes (e.g **6e**) have an asymmetric unit (A.U.) in which metal is coordinated by two molecules of sulfonamido-quinoline moieties and contain also a molecule of methanol as solvent (S). In the packing structure there is a tight array between the complex **6e** molecules with the methanol solvent molecules, which are occupying the free spaces in the packing crystals). The Cd^{2+} complexes (e.g **5d**) have an A.U. in which metal is coordinated by two molecules of sulfonamido-quinoline moieties and one molecule of water (W). In the packing structure each molecule of Cd^{2+} complex interracts with other two by intermolecular H-bond *via* coordinated water, stabilising its structure. The antibacterial and antifungal activity of compounds were studied. It was noticed that the compounds have only antibacterial activity, the presence in **HQBSM** molecules of a 4-chlorophenyl moiety and of Ni^{2+} (as divalent metal) being determinant for the antibacterial activity.

Crystallographic Information: More information regarding the structure of the interest molecules can be found in the crystallographic information file (.cif) registered in the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under deposition codes: 2,244,980 for complex **6a**, 2,244,979 for complex **6e** and 2,244,981 for complex **5d**.

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Data availability statement

The data associated with this study have been NOT deposited into a publicly available repository.

Table 6
The antibacterial and antifungal activity assay for the ligands **3b** and **3c** and the complexes **4e** and **4f**, **5a-f** and **6a-f** determined by disk diffusion assay.

	4e	4f	3 b	5a	5 b	5c	5 d	5e	5f	3c	6a	6 b	6c	6 d	6e	6f	C+	C-
S.aureus	11 ± 1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15 ± 1.5	0
E.coli	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15 ± 1.8	0
C.albicans	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16 ± 1.4	0

S. aureus: Staphylococcus. Aureus ATCC 25923; *E. coli: Escherichia coli ATCC 25922*; *C. albicans: Candida albicans ATCC 10231;* X±SD mean of five mesearurements ± standard deviation.
C+: Gentamicin for *S. aureus* and *E. coli; C-*: Nystatin for *C. albicans*.

Table 7
The minimum inhibitory concentration (MIC) for the complex [Ni(*N*-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$] compound **4e**.

	MIC (μg/mL)	
	4e	C+
S.aureus	0.78	0.5
E.coli	–	–
C.albicans	–	–

S. aureus: Staphylococcus. Aureus ATCC 25923; *E. coli: Escherichia coli ATCC 25922*; *C. albicans: Candida albicans ATCC 10231*.C+: Gentamicin for *S. aureus* and *E. coli.*

The data from Table 7, indicate that the complex [Ni(*N*-(quinoline-8-yl)-4-chloro-benzenesulfonamide)$_2$], **4e** is active, having a MIC of 0.78 μg/mL.

CRediT authorship contribution statement

Dumitrela Diaconu: Writing – review & editing, Visualization, Validation, Methodology, Investigation. **Violeta Mangalagiu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation. **Simona Dunca:** Writing – review & editing, Investigation. **Dorina Amariucai-Mantu:** Validation, Investigation. **Vasilichia Antoci:** Methodology, Investigation. **Tiberiu Roman:** Investigation. **Ionel I. Mangalagiu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ionel Mangalagiu reports was provided by Alexandru Ioan Cuza University.

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Appendix A. Supplementary data

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