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Synthesis, molecular structure and biological activity of Ni^{II} complexes based on substituted 2-(2-hydroxyphenyl)benzoxazole

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Contents

Experimental

Methods and materials

IR, NMR and electronic spectra were recorded using the equipment of the ‘Molecular Spectroscopy’ Center for collective use of the Southern Federal University.

NMR spectra were recorded on a Varian Unity-300 spectrometer. IR spectra of the samples were taken on a Varian 3100FT-IR Excalibur instrument using the method of disturbed total internal reflection (DTIR). Electronic absorption spectra were recorded on the Cary 50 Varian spectrophotometer at room temperature for solutions with $C = 2 \times 10^{-5}$ M.

The elemental analysis was performed on an automatic C, H, N, S analyzer Euro EA-3000 (EuroVektor) at the Central institute of the general and organic chemistry of the Russian Academy of Sciences. The melting point was measured on a Fisher–Jones device.

Synthesis of new coordination compounds was carried out in acetonitrile (> 99%) in air using $Ni(AcO)_2 \cdot 4H_2O$ (98+%, Alfa Aesar).

2-(3,4-Dichloro-6-hydroxy-2-methoxycarbonylphenyl)benzoxazole (**1a**), 2-(3,4-dichloro-2-ethoxycarbonyl-6-hydroxyphenyl)benzoxazole (**1b**), 2-(3,4-dichloro-6-hydroxy-2-isopropoxycarbonylphenyl)benzoxazole (**1c**) were obtained as described.[S1,S2]

A general method for the synthesis of Ni^{II} **2a–c** complexes.

A suspension of 0.037 g (0.15 mmol) $Ni(AcO)_2 \cdot 4H_2O$ in 10 ml of acetonitrile was added to the hot solution of the corresponding ligand **1a–c** (0.3 mmol) in 10 ml of acetonitrile. The solution instantly changed color from colorless to green and gradually began to precipitate. The reaction mixture was stirred at a temperature of 70 °C for 2 h. The precipitate was filtered off, washed 3 times with 5 ml of hot acetonitrile and 2 times with 5 ml of hexane and then dried in air to a constant mass.

Bis[2-(1,3-benzoxazole-2-yl-κ*N*)-4,5-dichloro-3-(methoxycarbonyl)phenolate-κ*O*]nickel(II) 2a. According to the method described above, 2-(3,4-dichloro-6-hydroxy-2-methoxycarbonylphenyl)benzoxazole **1a** (0.10 g, 0.3 mmol) was used to afford 0.10 g (92%) of the product **2a** as a light green powder (mp > 300 °C). ^{1}H NMR (300 MHz, DMSO-*d*$_6$), δ, ppm: 4.09 (br.s, 3H, OCH_3), 7.21 (br.s, H_{arom}), 8.31 (br.s, $H_{arom.}$). IR spectrum (ν, cm^{-1}): 1750, 1717, 1660, 1607, 1576, 1523, 1504, 1477, 1455, 1435, 1417, 1383, 1348, 1324, 1314, 1285, 1253, 1231, 1211, 1177, 1147, 1108, 1072, 1017, 1003, 974, 955, 908, 874, 861, 829, 788, 773, 750, 738, 710, 694, 666, 638, 616, 596, 578, 549, 516, 497, 461, 446, 423. Found (%): C 50.20; H 2.30; N 3.90. $C_{30}H_{16}Cl_4N_2NiO_8$. Calculated (%): C 49.16; H 2.20; N 3.82.

Bis[2-(1,3-benzoxazole-2-yl-κ*N*)-4,5-dichloro-3-(ethoxycarbonyl)phenolate-κ*O*]nickel(II) 2b. According to the method described above, 2-(3,4-dichloro-2-ethoxycarbonyl-6-hydroxyphenyl)benzoxazole **1b** (0.11 g, 0.3 mol) was used to afford 0.10 g (88%) of the product **2b** as a light green powder (mp > 300 °C). ^{1}H NMR (300 MHz, DMSO-*d*$_6$), δ, ppm: 1.43 (br.s, 3H, CH_3), 4.55 (br.s, 2H, CH_2), 7.22 (br.s, H_{arom}), 8.29 (br.s, $H_{arom.}$). IR spectrum (ν, cm^{-1}): 1721, 1700, 1607, 1575, 1525, 1503, 1455, 1436, 1419, 1369, 1327, 1284, 1254, 1230, 1181, 1149, 1108, 1084, 1065, 1024, 1003, 993, 970, 932, 911, 888, 857, 834, 785, 769, 751, 738, 714, 692, 667, 638, 615, 600, 585, 547, 516, 499, 468, 433. Found (%:) C 51.20; H 2.80; N 3.80. $C_{32}H_{20}Cl_4N_2NiO_8$. Calculated (%): C 50.50; H 2.65; N 3.68.

Bis[2-(1,3-benzoxazole-2-yl-κ*N*)-4,5-dichloro-3-(isopropoxycarbonyl)phenolate-κ*O*]nickel(II) 2c. According to the method described above, 2-(3,4-dichloro-6-hydroxy-2-isopropoxycarbonylphenyl)benzoxazole (0.11 g, 0.3 mol) was used to afford (0.10 g, 85%) of the product **2c** as a light green powder (mp > 300 °C). ^{1}H NMR (300 MHz, DMSO-*d*$_6$), δ, ppm: 1.42 (br.s, 6H, $2CH_3$), 5.41 (br.s, H, CH), 7.24 (br.s, H_{arom}), 8.28 (br.s, $H_{arom.}$). ИК спектр (ν, см$^{-1}$): 1727, 1697, 1604, 1575, 1522, 1505, 1458, 1449, 1426, 1386, 1365, 1351, 1340, 1324, 1283, 1263, 1250, 1236, 1185, 1155, 1101, 1072, 1017, 971, 920, 904, 851, 839, 783, 770, 736, 709, 692, 660, 640, 615, 592, 547, 514, 501, 471, 445, 419. Found (%): C 52.60; H 3.20; N 3.70. $C_{34}H_{24}Cl_4N_2NiO_8$. Calculated (%): C 51.75; H 3.07; N 3.55.

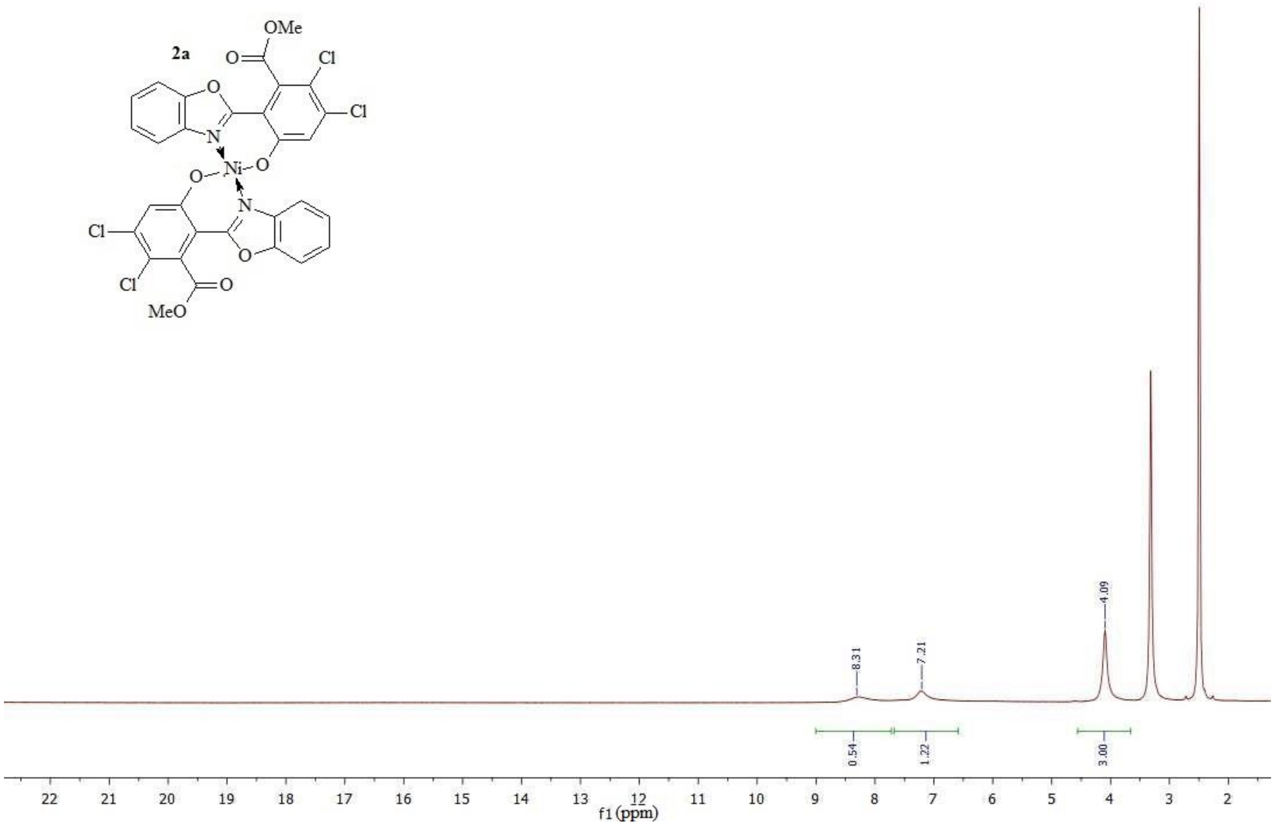


Figure S1 ^{1}H NMR spectrum of complex Ni^{II} **2a** in DMSO-d$_6$.

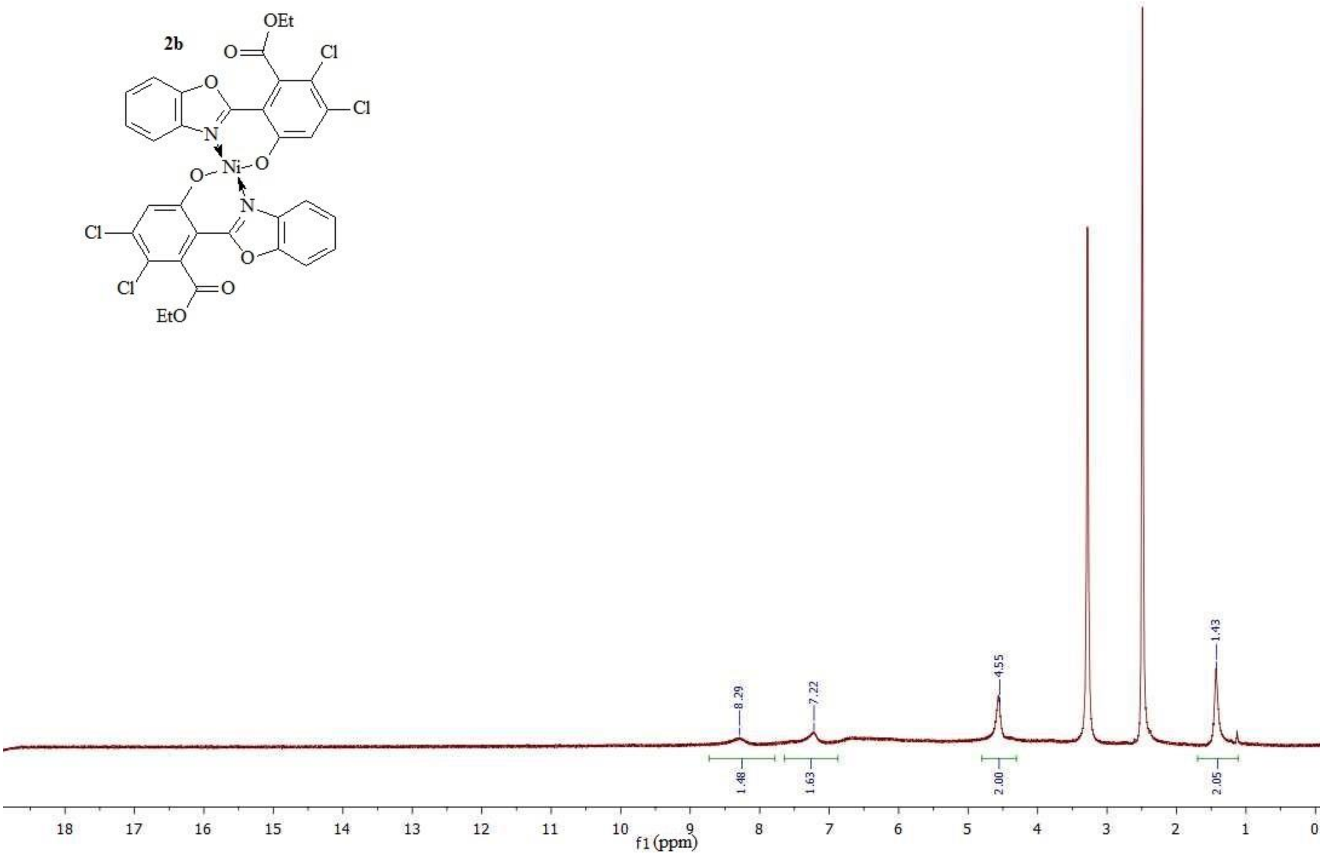


Figure S2 ^{1}H NMR spectrum of complex Ni^{II} **2b** in DMSO-d$_6$.

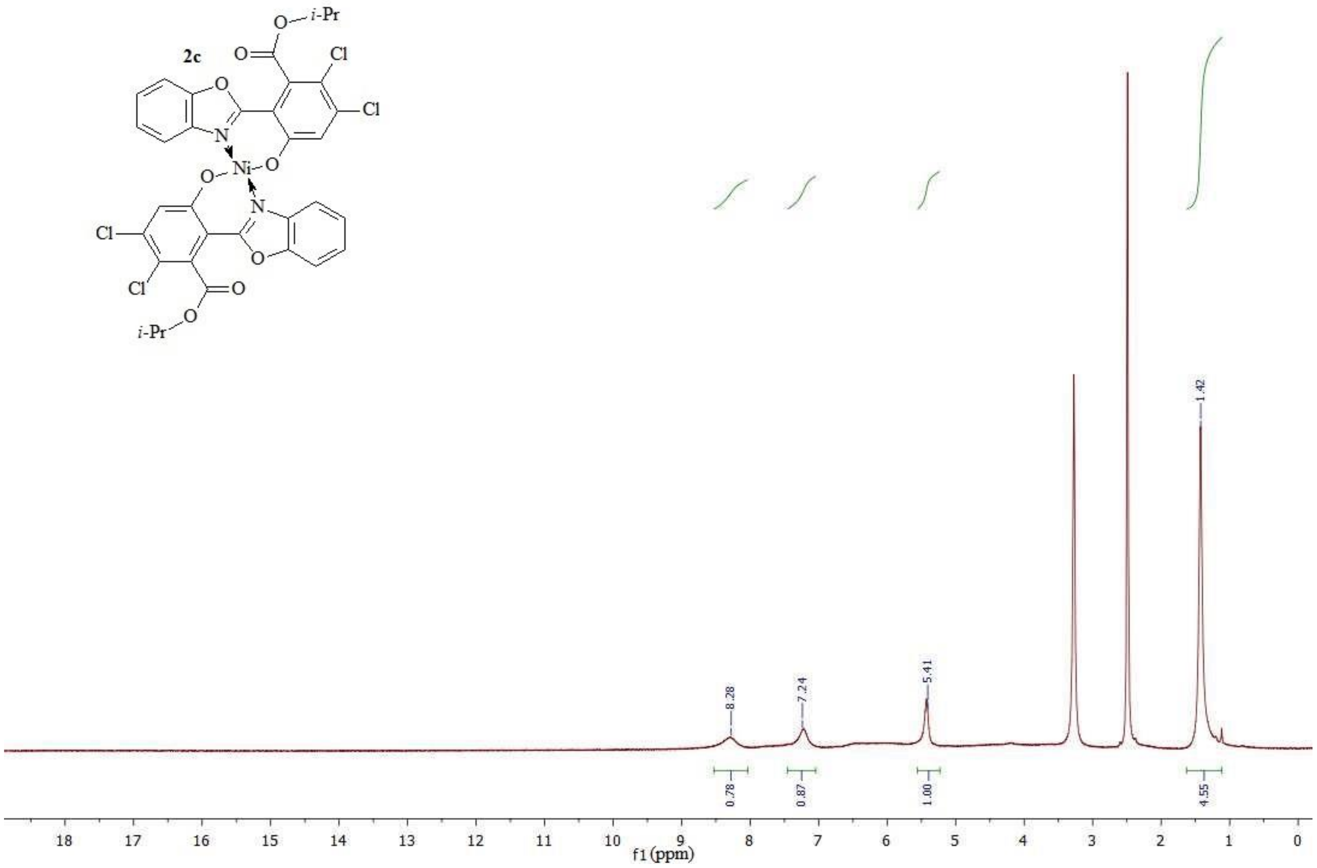
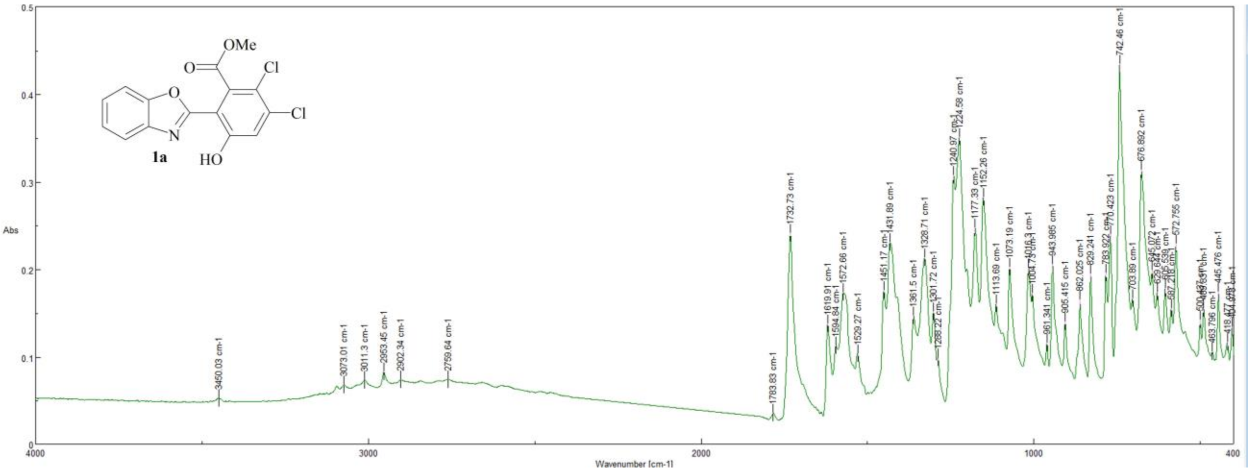


Figure S3 ^{1}H NMR spectrum of complex Ni^{II} **2c** in DMSO-d$_6$.

(*a*)



(*b*)

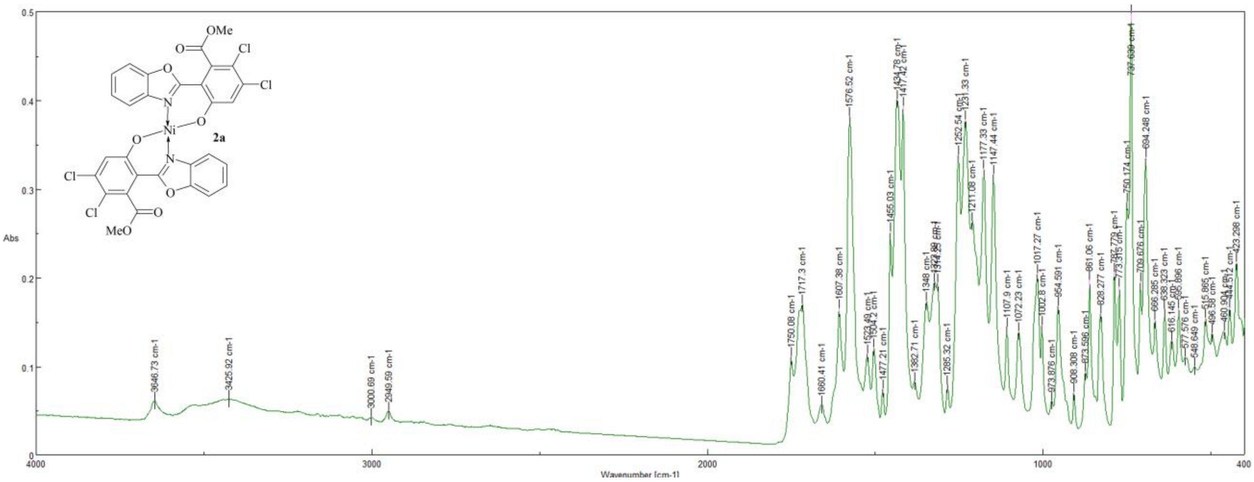


Figure S4 IR spectra of (*a*) ligand **1a** and (*b*) complex Ni^{II} **2a.**

(*a*)

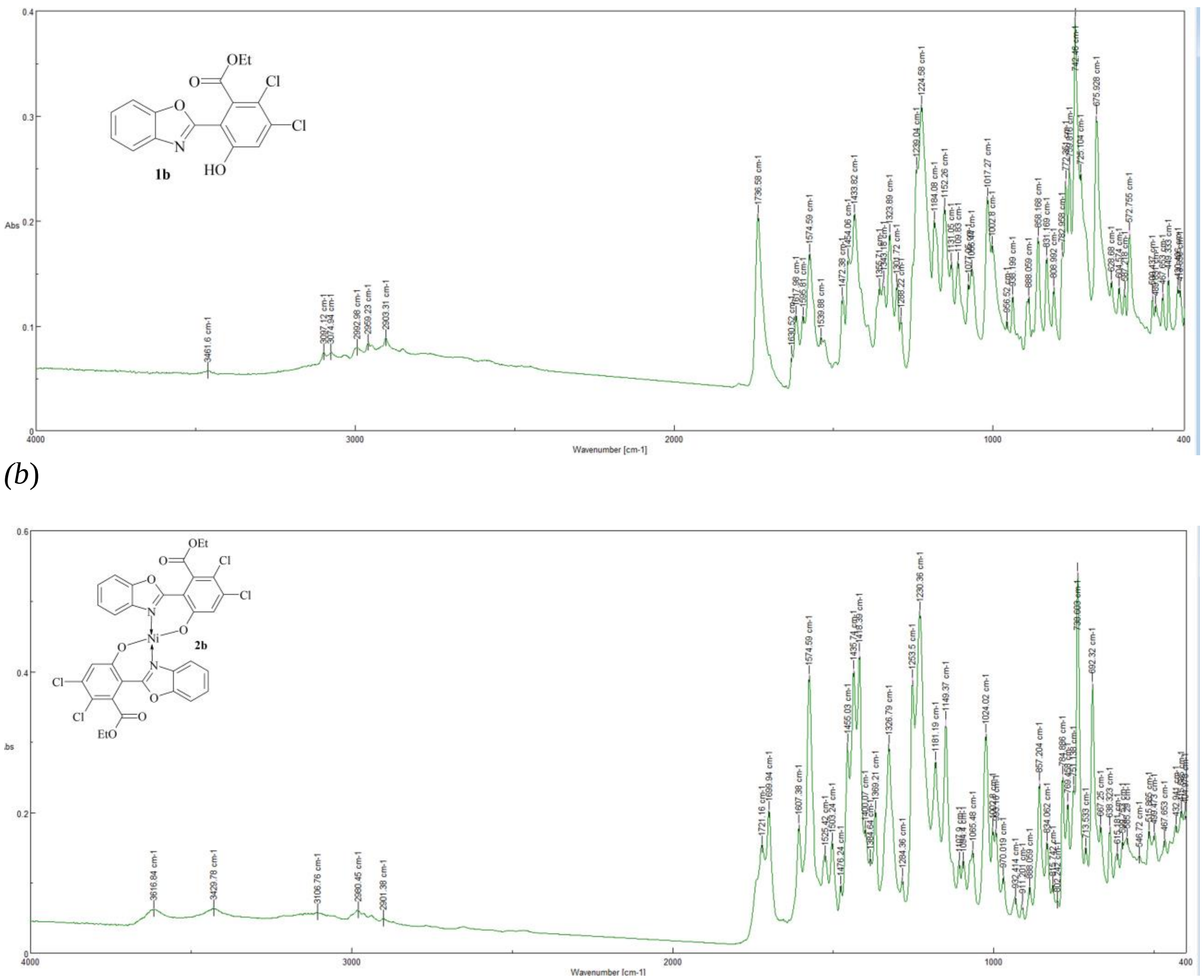


Figure S5 IR spectra of (*a*) ligand **1b** and (*b*) complex Ni^{II} **2b**.

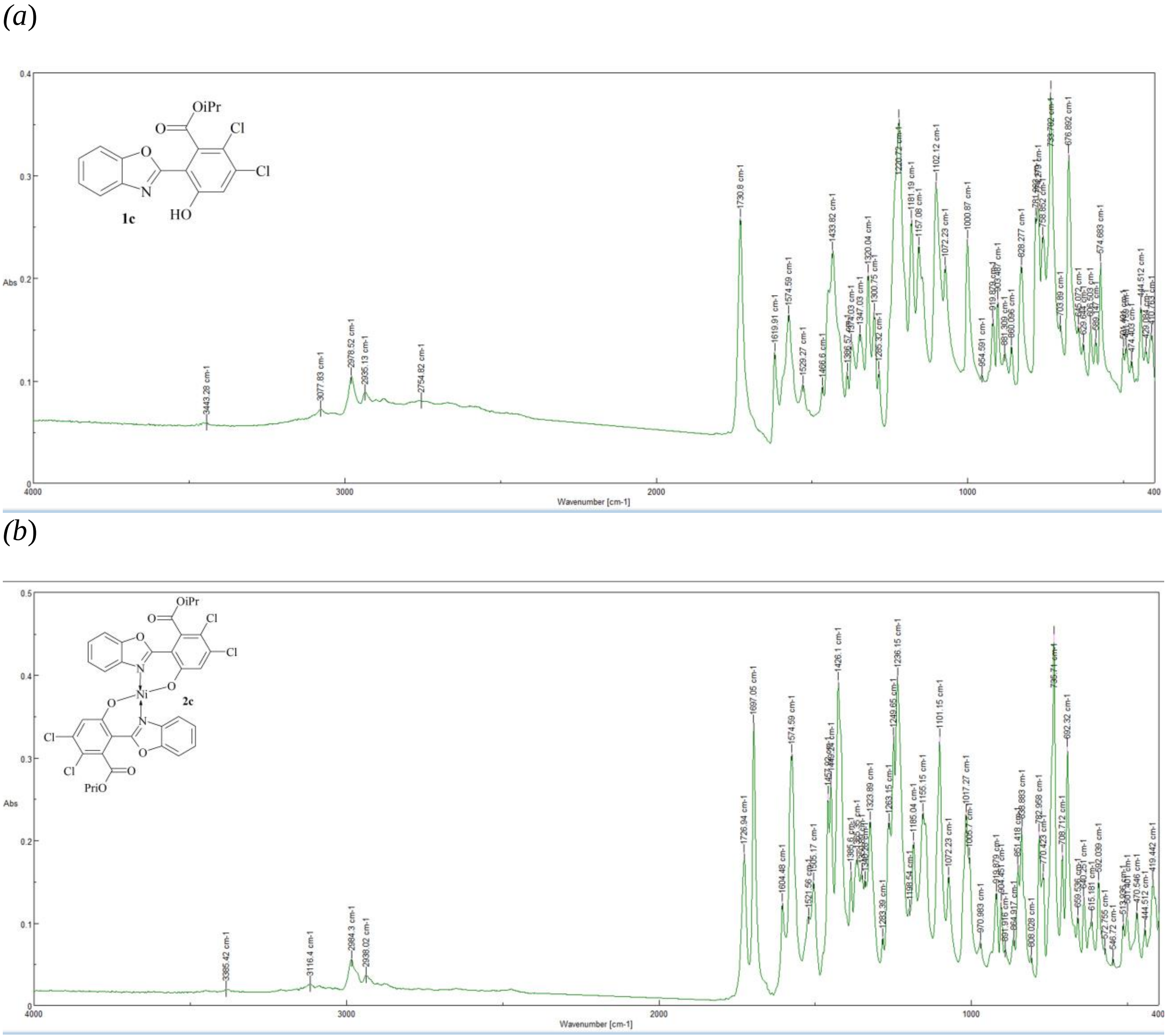


Figure S6 IR spectra of (*a*) ligand **1c** and (*b*) complex Ni^{II} **2c**.

X-ray diffraction analysis

Crystals of the Ni^{II} **2a** complex, suitable for PCA, were obtained by crystallization from a saturated dimethyl sulfoxide solution. A set of experimental data was obtained by an Agilent SuperNova diffractometer using a microfocus X-ray source with a copper anode and an Atlas[S2] coordinate CCD detector. Reflections collection as well as determination and refinement of unit cell parameters were carried out using a specialized software package CrysAlisPro (Rigaku Oxford Diffraction, 2015).[S3] Structures were decoded using the ShelXT program,[S4] ShelXL refinement;[S5] molecular graphics and preparation of material for publication were performed using the Olex2 software package.[S6] Complete X-ray structural data were deposited in the Cambridge Structural Data Bank [CCDC 2166674 (compound **2a**)].

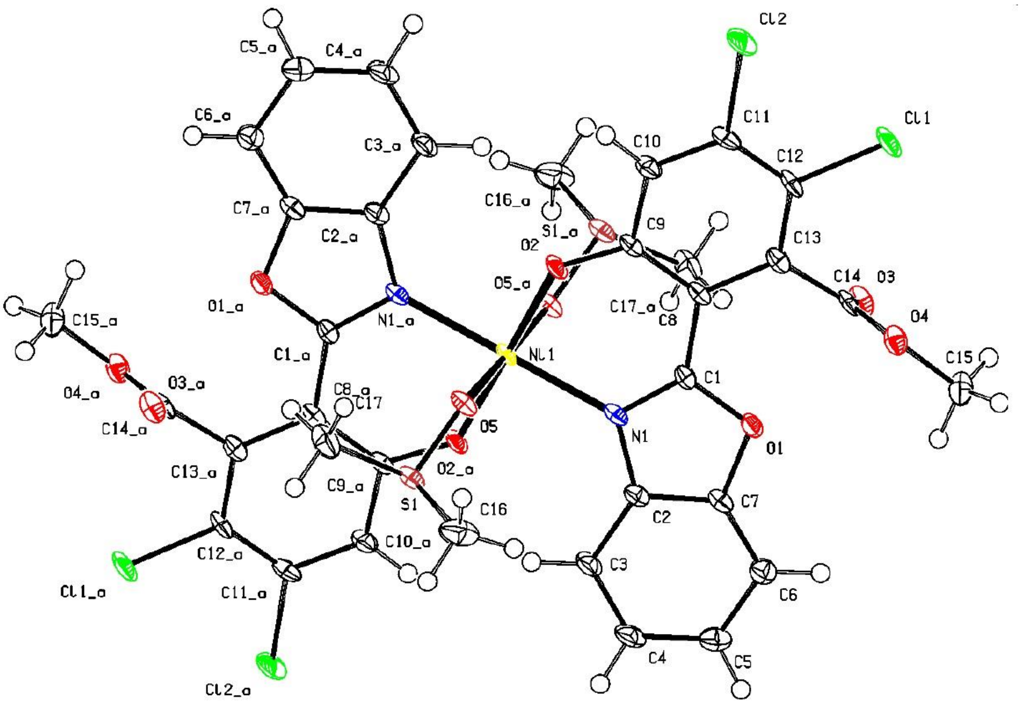


Figure S7 Molecular structure of complex **2a**

Table S1 Crystal data and structure refinement for **2a**.

CCDC Number	2166674
Empirical formula	$C_{34}H_{28}Cl_4N_2NiO_{10}S_2$
Formula weight	889.21
Temperature/K	99.98(18)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.6083(2)
b/Å	7.8650(2)
c/Å	21.3907(4)
α/°	90
β/°	95.427(2)
γ/°	90
Volume/Å^3	1776.72(7)
Z	2
ρ_{calc}g cm^{-3}	1.662
μ/mm^{-1}	5.192
F(000)	908.0
Crystal size/mm^3	0.362 × 0.285 × 0.195

Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.304 to 152.668
Index ranges	$-13 \leqslant h \leqslant 11; -9 \leqslant k \leqslant 9, -26 \leqslant l \leqslant 26$
Reflections collected	18293
Independent reflections	3681 [R_{int} = 0.0680, R_{sigma} = 0.0408]
Data/restraints/parameters	3681/0/244
Goodness-of-fit on F^2	1.045
Final R indexes [$I >= 2\sigma(I)$]	R_1 = 0.0474, wR_2 = 0.1257
Final R indexes [all data]	R_1 = 0.0513, wR_2 = 0.1294
Largest diff. peak/hole / e Å^{-3}	1.62/–0.58

Table S2 Bond lengths for complex **2a**.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Ni1	O2	2.0015(17)	O2	C9	1.288(3)	C2	C3	1.399(3)
Ni1	O2[1]	2.0016(17)	O1	C1	1.368(3)	C9	C10	1.431(3)
Ni1	O5	2.1192(18)	O1	C7	1.377(3)	C9	C8	1.435(4)
Ni1	O5[1]	2.1192(18)	O4	C14	1.333(3)	C13	C14	1.497(4)
Ni1	N1	2.066(2)	O4	C15	1.452(3)	C13	C8	1.416(3)
Ni1	N1[1]	2.066(2)	O3	C14	1.205(3)	C13	C12	1.378(4)
S1	O5	1.5142(18)	N1	C1	1.313(3)	C10	C11	1.370(4)
S1	C17	1.783(3)	N1	C2	1.402(3)	C3	C4	1.391(4)
S1	C16	1.782(3)	C1	C8	1.451(3)	C6	C5	1.392(4)
Cl1	C12	1.741(3)	C7	C2	1.390(4)	C11	C12	1.398(4)
Cl2	C11	1.737(3)	C7	C6	1.382(4)	C4	C5	1.404(4)

[1] 2–X,1–Y,1–Z

Table S3 Bond angles for complex **2a**.

Atom	Atom	Atom	Angle/°
O2	Ni1	O2^{1}	180.0
O2	Ni1	O5	85.76(7)
O2^{1}	Ni1	O5	94.24(7)
O2	Ni1	O5^{1}	94.24(7)
O2^{1}	Ni1	O5^{1}	85.76(7)
O2	Ni1	N1	86.15(8)
O2	Ni1	N1^{1}	93.84(8)
O2^{1}	Ni1	N1^{1}	86.16(8)
O2^{1}	Ni1	N1	93.85(8)
O5^{1}	Ni1	O5	180.0
N1^{1}	Ni1	O5	88.35(8)
N1	Ni1	O5^{1}	88.34(8)
N1	Ni1	O5	91.66(8)
N1^{1}	Ni1	O5^{1}	91.65(8)
N1	Ni1	N1^{1}	180.0
O5	S1	C17	104.57(13)
O5	S1	C16	105.04(13)
C16	S1	C17	98.26(17)
C9	O2	Ni1	128.92(17)
C1	O1	C7	104.88(19)
S1	O5	Ni1	128.24(11)
C14	O4	C15	115.0(2)
C1	N1	Ni1	123.37(18)
C1	N1	C2	105.0(2)
C2	N1	Ni1	130.34(17)
O1	C1	C8	117.6(2)
N1	C1	O1	114.1(2)
N1	C1	C8	128.2(2)
O1	C7	C2	107.9(2)
O1	C7	C6	127.9(2)
C6	C7	C2	124.3(2)
C7	C2	N1	108.1(2)
C7	C2	C3	120.3(2)
C3	C2	N1	131.6(2)
O2	C9	C10	117.6(2)
O2	C9	C8	125.2(2)
C10	C9	C8	117.2(2)
C8	C13	C14	121.4(2)
C12	C13	C14	117.3(2)
C12	C13	C8	120.9(3)
O4	C14	C13	112.6(2)
O3	C14	O4	125.2(3)
O3	C14	C13	122.2(2)
C11	C10	C9	121.1(3)
C9	C8	C1	119.0(2)
C13	C8	C1	121.3(2)
C13	C8	C9	119.6(2)
C4	C3	C2	116.3(3)
C7	C6	C5	115.3(3)
C10	C11	Cl2	118.0(2)
C10	C11	C12	121.3(2)
C12	C11	Cl2	120.7(2)
C13	C12	Cl1	120.0(2)
C13	C12	C11	119.6(2)
C11	C12	Cl1	120.3(2)
C3	C4	C5	122.3(3)
C6	C5	C4	121.5(3)

^{1} 2–X,1–Y,1–Z

Table S4 Torsion Angles for complex **2a**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Ni1	O2	C9	C10	162.21(18)	C2	C7	C6	C5	–1.6(4)
Ni1	O2	C9	C8	–18.0(4)	C2	C3	C4	C5	–0.2(4)
Ni1	N1	C1	O1	–166.57(16)	C9	C10	C11	Cl2	179.4(2)
Ni1	N1	C1	C8	16.0(4)	C9	C10	C11	C12	0.2(4)
Ni1	N1	C2	C7	165.48(18)	C14	C13	C8	C1	12.6(4)
Ni1	N1	C2	C3	–15.8(4)	C14	C13	C8	C9	–170.4(2)
Cl2	C11	C12	Cl1	–4.1(4)	C14	C13	C12	Cl1	–3.1(4)
Cl2	C11	C12	C13	178.2(2)	C14	C13	C12	C11	174.6(3)
O2	C9	C10	C11	–176.5(3)	C10	C9	C8	C1	171.8(2)
O2	C9	C8	C1	–8.0(4)	C10	C9	C8	C13	–5.3(4)
O2	C9	C8	C13	174.9(2)	C10	C11	C12	Cl1	175.1(2)
O1	C1	C8	C9	–169.3(2)	C10	C11	C12	C13	–2.6(4)
O1	C1	C8	C13	7.8(4)	C8	C9	C10	C11	3.6(4)
O1	C7	C2	N1	1.0(3)	C8	C13	C14	O4	–103.0(3)
O1	C7	C2	C3	–177.9(2)	C8	C13	C14	O3	78.0(3)
O1	C7	C6	C5	179.5(3)	C8	C13	C12	Cl1	–176.9(2)
N1	C1	C8	C9	8.0(4)	C8	C13	C12	C11	0.8(4)
N1	C1	C8	C13	–174.9(3)	C3	C4	C5	C6	1.6(5)
N1	C2	C3	C4	179.4(3)	C6	C7	C2	N1	–178.0(3)
C1	O1	C7	C2	–0.1(3)	C6	C7	C2	C3	3.0(4)
C1	O1	C7	C6	179.0(3)	C12	C13	C14	O4	83.3(3)
C1	N1	C2	C7	–1.6(3)	C12	C13	C14	O3	–95.7(3)
C1	N1	C2	C3	177.1(3)	C12	C13	C8	C1	–173.9(2)
C7	O1	C1	N1	–1.1(3)	C12	C13	C8	C9	3.1(4)
C7	O1	C1	C8	176.6(2)	C15	O4	C14	O3	–6.3(4)
C7	C2	C3	C4	–2.0(4)	C15	O4	C14	C13	174.7(2)
C7	C6	C5	C4	–0.7(4)	C17	S1	O5	Ni1	–123.23(16)
C2	N1	C1	O1	1.7(3)	C16	S1	O5	Ni1	133.85(17)
C2	N1	C1	C8	–175.7(3)					

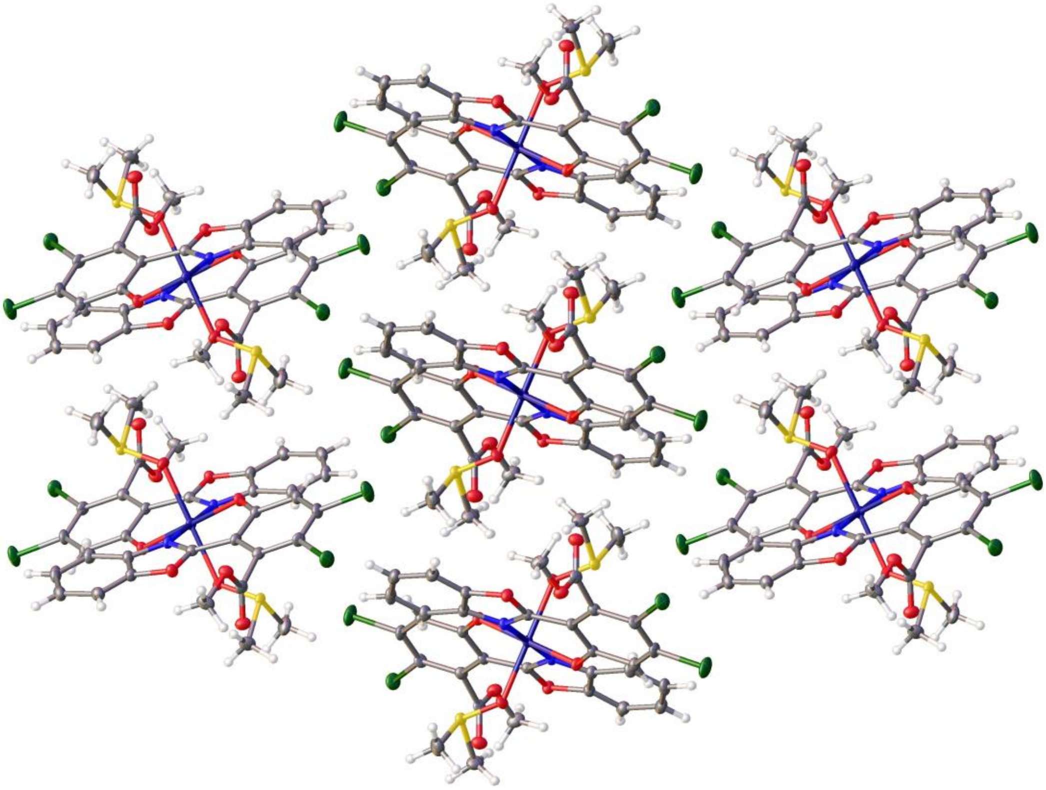


Figure S8 Fragment of the molecular packaging of complex **2a**.

Biologic studies

Antibacterial activity was studied on dense nutrient media *via* diffusion into agar. Discs of a diameter 6 mm made of filter cardboard were used to determine sensitivity to antimicrobial drugs (ND-PMP-1) produced by the Pasteur Research Institute of Epidemiology and Microbiology (St. Petersburg).

At the first stage (screening of active compounds), two cultures were used: *E. coli* VKM B-820 and *St. aureus* VKM B-128. Solutions of the tested compounds were applied to the discs. The load of each connection was 15 micrograms per disk. The disks were placed on the lawn of a bacterial culture sown on nutrient agar in Petri dishes by flushing a daily bacterial culture with a density of 5 units according to the optical standard. The activity of the compounds was assessed by the size of the growth retardation zone of the bacterial culture. The comparison drugs were furazolidone and ciprofloxacin. The method (modification of SKZNIVI) has been described earlier.[S7,S8]

The study of the fungistatic activity of the new substances was carried out on the culture of fungi of the genus *Penicillium*, the species *Penicillium italicum Wehmer* (1894), the reference strain VKM F-1279. The method (modification of SKZNIVI) has been described earlier.[S8] The comparator drug was fundazole.

Protistocidal activity was studied on protozoa of the species *Colpoda steinii* (field isolate), a collection of the Laboratory of Parasitology of SKZNIVI. The protistocidal activity was studied by the method of serial dilutions according to the developed methodology.[S9] Comparator drugs were: aqueous solutions of a certain concentration prepared from Baycox™, 2.5% toltrazuril solution (international nonproprietary name), and Chloroquine (delagil) in the form of aqueous solutions of the same concentrations as the tested compounds.

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