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Synthesis, characterization, antibacterial activities and carbonic anhydrase enzyme inhibitor effects of new arylsulfonylhydrazone and their Ni(II), Co(II) complexes

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ABSTRACT

Ethane sulfonic acide hydrazide (*esh*: $CH_3CH_2SO_2NHNH_2$) derivatives as 5-methylsalicyl-aldehyde-ethanesulfonylhydrazone (*5msalesh*), 5-methyl-2-hydroxyacetophenoneethane sulfonylhydrazone (*5mafesh*) and their Ni(II), Co(II) complexes have been synthesized for the first time. The structure of these compounds has been investigated by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, LC/MS, UV–vis spectrophotometric method, magnetic susceptibility, thermal studies and conductivity measurements. The antibacterial activities of synthesized compounds were studied against Gram positive bacteria; *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus magaterium* and Gram negative bacteria; *Salmonella enteritidis*, *Escherichia coli* by using the microdilution broth method. The biological activity screening showed that ligands have more activity than complexes against the tested bacteria. The inhibition activities of these compounds on carbonic anhydrase II (CA II) have been investigated by comparing IC_{50} and K_i values and it has been found that *5msalesh* and its complexes have more enzyme inhibition efficiency than other compounds.

1. Introduction

Sulfonylhydrazones, derivatives of sulfonamide, exhibit several medicinal applications. For example, benzaldehyde arylsulfonylhydrazones possess antineoplastic activity against human stomach cancer SGC 7901 [1], 4-substituted benzenesulfonylhydrazone has been studied for antibacterial activities [2], N-arylsulfonylhydrazones have been identified as novel inhibitors of IMP-1, a metallo-β-lactamase enzyme [3]. In addition, the unsubstituted aromatic sulfonamides act as carbonic anhydrase inhibitors CAIs [4,5], whereas other types of derivatives show diuretic activity (high-ceiling diuretics or thiadiazine diuretics), hypoglycemic activity, anticancer properties, [6] or may act as inhibitors of the aspartic HIV protease, being used for the treatment of AIDS and HIV infection among others. CA inhibitors can serve as useful therapeutic agents for treating numerous diseases, including glaucoma, cancer and obesity [7–9].

The first sulfonamide metal complex used as drug was the silver(I) derivative of sulfanilamide [10]. Later on, many other metal complexes of sulfanilamide analogues were subsequently synthesized and investigated for biological activity in detail [11]. Transition metal complexes of hydrazides and sulfonamides also find application in chemotherapy as well as their hydrazone derivatives [12].

In our previous studies, we reported the antibacterial and cytotoxic effect of methanesulfonic acid hydrazide and its hydrazone derivatives [13], as well as its metal carbonyl complexes [14]. Synthesis of metal carbonyl complexes of the sulfonylhydrazones was also reported [15–17]. Furthermore, methane and propanesulfonylhydrazone derivatives and their transition metal complexes were synthesized and screened for antimicrobial activity [18,19].

As part of our ongoing studies, new ethanesulfonylhydrazone derivatives and their Ni(II) and Co(II) complexes were obtained and characterized by spectroscopic method. The antibacterial activities of our compounds were screened against several bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus magaterium*, *Salmonella enteritidis*, *Escherichia coli*) by using the microdilution broth method. In addition, their inhibitory effects on carbonic anhydrase II (CA II) enzyme were investigated.

2. Experimental

2.1. Physical measurements

The solvents used were purified and distilled according to routine procedures. Ethanesulfonyl chloride, hydrazine hydrate, 5-methylsalicylaldehyde, 5-methyl-2-hydroxyacetophenone and

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anhydrous nickel and cobalt chloride were commercial products (Purum). Elemental analyses were performed according to standard microanalytical procedures (TÜBİTAK Laboratories, Ankara). ^1H and ^{13}C NMR spectra of dimethylsulfoxide-d_6 (DMSO-d_6) solutions of the compounds were registered on a Bruker WM-400 spectrometer (400 MHz) using tetramethyl silane as internal standard. D_2O-exchange was applied to confirm the assignment of the NH- and OH-signals. The infrared spectra of the compounds as KBr-disks were recorded in the range of 4000–400 cm^{-1} with a Mattson 1000 FT spectrometer. UV–vis spectra were recorded on T 80+ UV–vis spectrometer. Melting points of sulfonylhydrazone derivative were determined with a Gallenkamp melting point apparatus. The molar magnetic susceptibilities were measured on powdered samples using Gouy method. The molar conductance measurements were carried out using a Siemens WPA CM 35 conductometer. A Du Pont Instrument 951 thermal analyzer was used to record simultaneously TG and DTA curves. The experiments were carried out in dynamic nitrogen atmosphere (20 mL min^{-1}) with a heating rate of 10 °C min^{-1} in the temperature range 30–400 °C using platinum crucibles. The microdilution broth method was used to determine the antibacterial activity of compounds against the bacteria; *S. aureus* ATCC 25923, *B. subtilis* RSKK 244, *B. magaterium* RSKK 5117, *S. enteritidis* ATCC 13076, *E. coli* ATCC 11230. Carbonic anhydrase activity was assayed by the hydrolysis of p-nitrophenylacetate. IC_{50} and K_i values of compounds were determined on CA II.

2.2. Synthesis of ligands

The solution of 1.10 g (10 mmol) ethanesulfonicacid hydrazide in 5 mL of ethanol was mixed with hot solution of 12 mmol of the corresponding aldehydes in 10 mL of ethanol and stirred for 1 h. Upon cooling, crystalline precipitates were filtered, washed with ethanol–ether, recrystallized from water and dried in vacuo over P_2O_5. They are colorless and light yellow crystalline solids, stable at normal conditions and soluble in methanol, ethanol, acetonitrile, dimethylformamide, DMSO; and poorly soluble in benzene and water.

2.3. Synthesis of Ni(II) and Co(II) complexes

All complexes are prepared by the following general method: a sample of anhydrous 0.53 mmol MCl_2, where M=Ni(II) and Co(II), were dissolved in a mixture of methanol and acetonitrile (25 mL), and a solution of hydrazone derivatives (1.60 mmol) in a mixture of acetonitrile (25 mL) and NaOH solution in methanol (1.60 mmol) was added. The reaction mixture was heated at 40 °C for 30 min and left in ice bath for 3 h. The solid complexes formed were collected by filtration, washed with a small volume of methanol and ether, and then, dried in a desiccator over $CaCl_2$.

2.4. Procedure for antibacterial activity

The in vitro antibacterial activity of the free ligands and their complexes was tested against the Gram positive bacteria; *S. aureus* ATCC 25923, *B. subtilis* RSKK 244, *B. magaterium* RSKK 5117 and Gram negative bacteria, *S. enteritidis* ATCC 13076, *E. coli* ATCC 11230. Minimum Inhibitory Concentrations (MIC's) were determined by the microdilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards [20,21]. MIC's were defined as the lowest concentrations of compounds which inhibit the growth of microorganisms. All tests were performed in Nutrient Broth (NB) dissolved in DMSO which lacked antibacterial activity against any of the test bacteria. The microplates were incubated at 37 °C and read visually after 24 h for MIC's [22]. The results were recorded according to the presence and absence of growth.

2.5. Procedure for CA II enzyme inhibitor activity

Carbonic anhydrase activity was assayed by the hydrolysis of p-nitrophenylacetate [23]. IC_{50} and K_i values of compounds were determined on CA II. In order to determine IC_{50} values, 1.2 mL of 3 mM p-nitrophenylacetate was used as substrate and three different concentrations (0.3, 0.6 and 1.2 mM) of inhibitors (*5mafesh* and its Ni(II), Co(II) complexes) were used. For *5msalesh* and its Ni(II), Co(II) complexes, 0.05, 0.025, 0.01 mM inhibitor concentrations were used. Reaction was started by adding 0.05 M Tris–SO_4 (pH 7.4) and 0.1 mL enzyme solution (0.17 mg/mL) for total volume of 3 mL. The absorbance was determined at 400 nm after 1 min. This study was repeated three times for each inhibitor. The inhibitor concentrations causing up to 50% inhibition were determined from the graphs. This method was applied to determine K_i values. In the media with or without inhibitor, the substrate concentrations were 0.3, 0.6 and 1.2 mM. For this aim, inhibitor solutions (*5mafesh* and its Ni(II), Co(II) complexes) were used for the reaction medium in three different concentrations (0.05, 0.025 and 0.01 mM). For *5msalesh* and its Ni(II), Co(II) complexes, 0.05, 0.025, 0.01 mM inhibitor concentrations were used. The Linewear–Burk graphs were obtained and K_i values were calculated.

3. Results and discussion

Analytical data and some physical properties of the sulfonylhydrazone derivatives and their Ni(II), Co(II) complexes are summarized in Table 1. The elemental analysis results show 1:2 (metal:ligand) stoichiometry for all the complexes. The analytical results are in good agreement with those required by the general formula $[(ML_2)(H_2O)_x]\cdot nH_2O$ (x = 0, 2; n = 0, 1 or 3). The molar conductivity (Λ_m) of 10^{-3} M solutions of the complexes in MeOH at 25 °C was measured and all the complexes were found non-electrolytic nature in the range of 2.6–4.7 Ω^{-1} cm^2 mol^{-1}.

3.1. Characterization of compounds

3.1.1. IR spectra

The important diagnostic IR bands of sulfonylhydrazones and their complexes are summarized in Table 2. Bands in the region of 3211 and 3215 cm^{-1} may be due to ν(NH) stretching vibration for

Table 1
Analytical and physical data for arylsulfonylhydrazones and their complexes.

Compound	Empirical formula (formula weight)	Color	m.p. (°C)	Yield (%)	Found (calculated)			
					%C	%H	%N	%S
5msalesh	$C_{10}H_{14}N_2SO_3$ 242.07	Yellow	119–120	50	9.48 (9.57)	5.66 (5.82)	11.34 (11.56)	13.00 (13.23)
5mafesh	$C_{11}H_{16}N_2SO_3$ 256.09	Yellow	108–110	55	51.23 (51.54)	6.02 (6.29)	10.58 (10.93)	12.20 (12.51)
Ni(*5msalesh*)$_2$	$C_{20}H_{26}N_4O_6S_2Ni$ 540.06	Green	250>	40	44.04 (44.38)	3.99 (4.84)	10.19 (10.35)	11.05 (11.85)
Ni(*5mafesh*)$_2$	$C_{22}H_{30}N_4O_6S_2Ni$ 569.32	Green	215>	45	45.49 (46.41)	5.01 (5.31)	9.04 (9.84)	11.05 (11.26)
[Co(*5msalesh*)$_2$(H_2O)$_2$]3H_2O	$C_{20}H_{36}N_4O_{11}S_2Co$ 631.50	Orange	240>	35	37.68 (38.03)	4.80 (5.75)	8.20 (8.87)	10.06 (10.15)
[Co(*5mafesh*)$_2$(H_2O)$_2$]H_2O	$C_{22}H_{36}N_4O_9S_2Co$ 622.90	Brown	240>	42	41.05 (42.37)	5.01 (5.82)	8.34 (8.98)	9.93 (10.28)

Table 2
Major IR absorption bands (cm^{-1}) of arylsulfonylhydrazones and their complexes.

Assignment	*5msalesh*	*5mafesh*	Ni-*5msalesh*	Co-*5msalesh*	Ni-*5mafesh*	Co-*5mafesh*
ν(NH)	3211s	3215s	3214w	–	3217s	3200s
ν(C=N)	1625m	1613s	1596s	1600m	1585s	1590m
$\nu_{as}(SO_2)$	1318s	1324s	1312s	1321w	1313s	1315s
ν(CO)	1269s	1257s	1307s	1289m	1295m	1281s
$\nu_s(SO_2)$	1147s	1152s	1155s	1147m	1153s	1148s
δ(NH)	691m	712s	680m	692m	708m	698s
$\delta(SO_2)$	528s	536s	529m	530m	534m	534m

5msalesh and *5mafesh*. The strong bands at 1625 and 1613 cm^{-1} are assigned to ν(C=N) stretching mode of the imine group for ligands. These bands are shifted to lower wavenumber in all complexes. This shifts support the participation of the imine group of these ligands in binding to the metal ions [24,25]. Ligands also display bands at 1269 and 1257 cm^{-1} which are assigned to ν(C–O) stretching vibrations for *5msalesh* and *5mafesh*, respectively. These bands are strongly affected by chelation through the phenolic–CO groups of the sulfonylhydrazone and the shift to higher wavenumbers indicates the coordination of phenolic–O donor atoms [26,27].

3.1.2. NMR spectra

^{1}H NMR and ^{13}C NMR data of DMSO-d_6 solutions of the sulfonylhydrazones are given in Table 3. The integration which is in accordance with 1:2 formulation proposed by elemental analyses, allowed the assignment of them. The comparison of spectra of ketone derivatives facilitates the distinguishing of the signals of the methyl protons from CH_3–C_6H_5 (*5msalesh* and *5mafesh*), CH_3C=N (*5mafesh*), and CH_3CH_2 (*5msalesh* and *5mafesh*) fragments, the assignment of the latter being accordance with the data from Refs. [18,19]. The position of the signal of the HC=N protons in the spectrum of *5msalesh* is in agreement with the data for other Schiff bases [19,28,29]. The signals of the HC=N and CH_3C=N protons show no splitting, and the positions of the signals of the ring protons are typical. In general, the multiplates observed at 6.78–7.74 and 6.67–7.23 ppm are assigned to *5msalesh* and *5mafesh* ring protons respectively. Signals at 9.95 and 11.12 ppm; 10.24 and 11.34 ppm are assigned to the NH and OH protons respectively for *5msalesh* and *5mafesh*. The highfield shift of NH protons may be due to the involvement of this group with a hydrogen bond in DMSO-d_6, which is well known for its interaction with an amide proton [30]. In the ^{1}H NMR spectrum of the Ni(II) complexes, the –OH-signals have disappeared indicating the coordination of phenolic –OH to the metal ion via deprotonation. The azomethine group has shifted to the downfield (0.28 ppm) region indicating coordination of >C=N to the metal ion. The other chemical shift values of complexes are very close to that of ligand proton. The ^{1}H NMR spectra of Co(II) complexes were not carried out due to paramagnetic.

The ^{13}C NMR spectra of *5msalesh* and *5mafesh*, the imine carbon resonances are found at 145.17 and 155.68 ppm as well as 154.70 and 157.52 ppm for C–O (phenolic –OH bounded) signals in aromatic field.

3.1.3. Mass spectra

Fragmentation steps of all complexes in LC–MS spectra are exhibited in Fig. 1. LC–MS spectra show that [Ni(*5msalesh*)$_2$], [Ni(*5mafesh*)$_2$], [Co(*5msalesh*)$_2$] and [Co(*5mafesh*)$_2$] give the molecular ions, $[ML_2]^+$ at the desired positions: *m*/*z* (intensity, %) = 538.9 (14.0), 569.0 (16.7), 539.0 (100.0) and 569.9 (20.1), $[ML]^{2+}$ fragments are observed at 299.1 (9.0), 313.0 (13.0), 301.0 (3.7) and 314.3 (5.0). The fragmentation of –N–NH–SO_2 C_2H_5 group in all complexes is observed at 121.0 with a wide range of intensities [19]. The fragmentation of C_8H_6 group is in accord with aldehyde in complexes which are observed at 101.1 (100%) as main peak except *Ni5msalesh* and *Co5mafesh*.

3.1.4. Electronic spectra and magnetic behavior

The significant electronic spectra of the complexes are recorded in methanol. The important bands of the ligands and the complexes are observed in the region of 295–265 and 340–300 nm. They may be attributed, respectively, to $\pi \rightarrow \pi^*$ type and charge–transfer transitions. The spectra of the Ni^{2+} complexes show bands in the range of 490–498 nm. Hence, square-planer structures may be assigned to these complexes [31]. Cobalt (II) complexes exhibit two bands between 572 and 751 nm suggesting an octahedral geometry.

The magnetic moments of complexes (as B.M.) were measured at room temperature. Nickel(II) complexes have diamagnetic characters, and therefore complexes have square-planer geometry. The magnetic moment values of cobalt (II) complexes are 4.72 and 5.01 B.M. respectively.

3.1.5. Thermal studies

Thermal behavior of complexes was determined in nitrogen atmosphere (20 mL min^{-1}) with a heating rate of 10 °C min^{-1} in the temperature range 30–400 °C. The thermogram of Ni(*5msalesh*)$_2$

Table 3
^{1}H–^{13}C NMR spectroscopic data for arylsulfonylhydrazones in DMSO-d_6 (ppm).

Compound	Assignment	^{1}H NMR	Assign.	^{13}C NMR
5msalesh	**CH_3**–CH_2	1.21(s, 3H)	**CH_3**–CH_2	8.24
	CH_3–C_6H_5	2.21(s, 3H)	**CH_3**–C_6H_5	20.47
	CH_2–SO_2	3.20(s, 2H)	**CH_2**–SO_2	45.13
	(**CH**)$_{Ar}$	6.78–7.74(m, H)	(**C**H)$_{Ar}$	116.53, 119.56, 127.33, 128.39, 132.44
	HC=N–	8.23(s, H)	**C**=N	145.17
	N**H**	9.95(s, H)	**C**–0	154.70
	O**H**	11.12(s, H)	–	–
5mafesh	**CH_3**–CH_2	1.15(s, 3H)	**CH_3**–CH_2	8.26
	CH_3–C=N	2.19(s, 3H)	**CH_3**–C=N	15.08
	CH_3–C_6H_5	2.14(s, 3H)	**CH_3**–C_6H_5	20.61
	CH_2–SO_2	3.12(s, 2H)	**CH_2**–SO_2	45.41
	(**CH**)$_{Ar}$	6.67–7.23(m, H)	(**C**H)$_{Ar}$	117.18, 120.31, 127.82, 129.07, 132.12
	N**H**	10.24(m, H)	**C**=N	155.68
	O**H**	11.34(s, H)	**C**–0	157.52

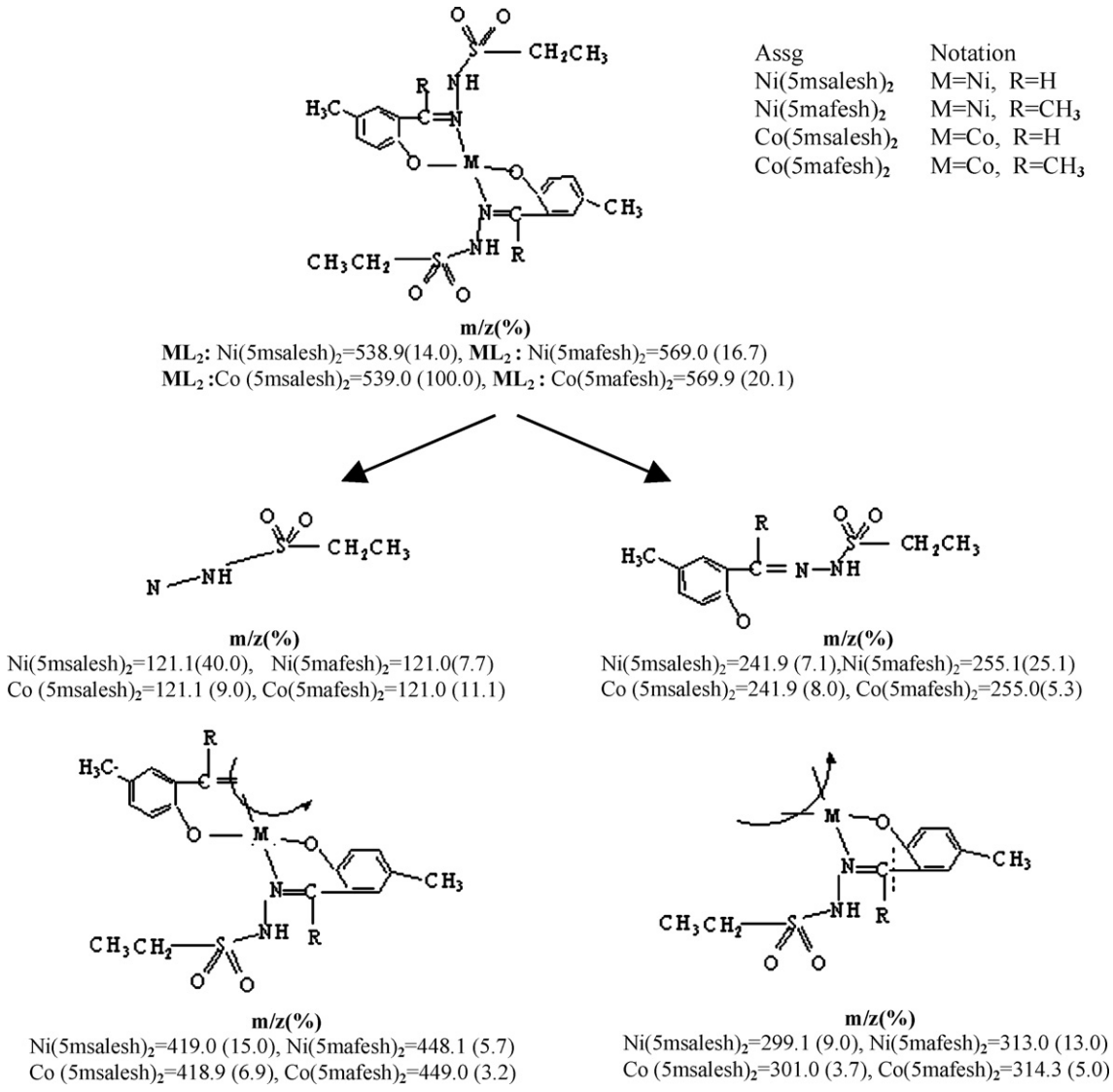

Fig. 1. Main fragmentation steps of Ni(II) and Co(II) complexes.

and Ni(*5mafesh*)$_2$ has no mass loss up to organic decomposition over 220 and 240 °C, this means that both complexes does not contain any coordinated or crystal water molecule [19]. In the thermogram of [Co(*5msalesh*)$_2$(H_2O)$_2$]3H_2O the first decomposition step by losing of three crystal water molecules is observed within a mass loss of 8.37% (calcd. 8.55%) at 90 °C and at second step within a mass loss of 5.45% (calcd. 5.70%) at 135 °C corresponds to the loss of two moles of coordinated water molecules. The thermogram of [Co(*5mafesh*)$_2$·2H_2O]H_2O shows decomposition at first step within a mass loss of 2.95% (calcd. 3.02%) at 88 °C and at second step within a mass loss of 5.44% (calcd. 5.78%) at 178 °C corresponds to the loss of one mole crystal and two moles coordinated water molecules [29,32].

3.2. Antibacterial activity results

The antibacterial activity of sulfonylhydrazone and their complexes was tested against microorganisms. The microorganisms used in the present investigations included bacteria; Gram positive bacteria *S. aureus* ATCC 25923, *B. subtilis* RSKK 244, *B. magaterium* RSKK 5117 and Gram negative bacteria, *S. enteritidis* ATCC 13076, *E. coli* ATCC 11230. The microdilution broth method was used to determine the antibacterial activity of the synthesized compounds [20]. The antibacterial results are given in Table 4.

The antibacterial results evidently show that the sulfonylhydrazones and their complexes posses a broad spectrum of activity against the tested bacteria at MIC values between 182 and

Table 4
The MIC's values of arylsulfonylhydrazones and their complexes (μg/mL).

Compounds	*B subtilus* RSKK 244	*B magatrium* RSKK 5117	*S. aureus* ATCC 25923	*S. enteritidis* ATCC 13076	*E. coli* ATCC 11230
5msalesh	286	260	182	242	208
5mafesh	291	266	260	266	266
Ni5msalesh	378	432	324	399	370
Co5msalesh	541	560	338	648	432
Ni5mafesh	472	433	325	472	392
Co5mafesh	627	570	374	649	456

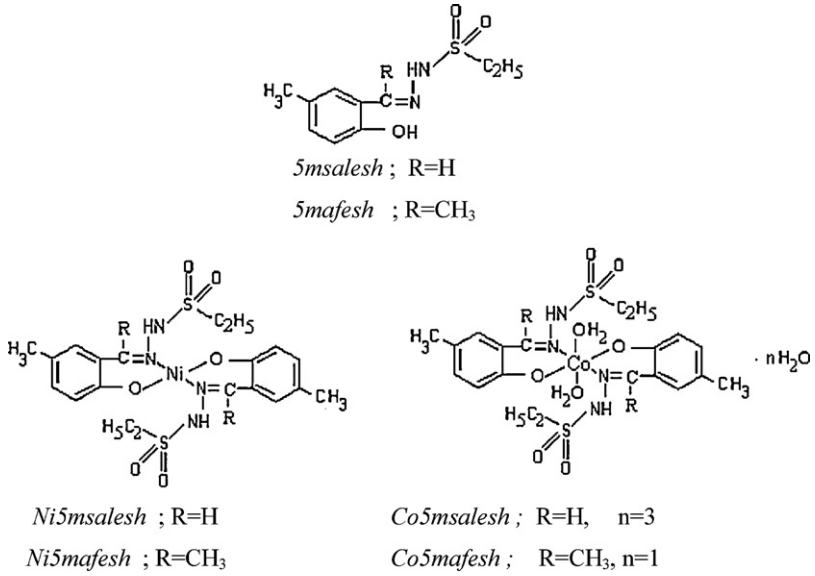

Fig. 2. Structures of arylsulfonylhydrazones and their complexes.

649 μg/mL. The ligands have more activity than complexes against the tested bacteria. The presence of electron densities on –SO_2NH– group in sulfonamide contributes positively to the increase of the activity of compounds against bacteria [33–36]. But the decrease of the electron densities by the coordination through the donor atoms causes a decrease of activities of complexes [19,37]. If ligands are compared with each other, *5msalesh* has more activity than *5mafesh* against the tested bacteria. A similar situation was reported in previous papers [18,19]. If complexes are compared with each other, Ni(II) complexes have more activity than Co(II) complexes [18]. All compounds have the most activity against *S. aureus* among all bacteria.

3.3. Carbonic anhydrase II (CA II) activity results

In this study, our aim was to determine the inhibitory effects of new ligands and their complexes. IC_{50} (IC_{50} represents the molarity of inhibiting a 50% decrease of enzyme activity) and K_i (inhibitor–enzyme dissociation constant) values were given in Table 5. As seen in Table 5, all the compounds behave as inhibitors against CA II enzyme, in addition, *5msalesh* and its complexes have higher inhibitor effects than *5mafesh* and its complexes on CA II. This result may be explained that *5msalesh* binds to enzyme active site through an additional hydrogen bond with imine C–H proton as well as van der Waals interaction. In recent years it has been established that a C–H group can be a hydrogen bond donor. Although considered weak in nature, the bond C–H. . .X (X: O, π) termed as C–H interaction is known to be distributed widely among protein structures [38]. Furthermore, our Ni(II) complexes have more inhibition effect than Co(II) complexes against CA II. Similar results were also reported by Supuran and co-workers [39].

Table 5
The result of inhibition studies for all compounds on carbonic anhydrase II.

Compounds	I_{C50} (mM)	K_i (mM)
5msalesh	0.05	0.06
5mafesh	1.10	1.60
Ni5msalesh	0.07	0.12
Co5msalesh	0.09	0.81
Ni5mafesh	1.25	1.75
Co5mafesh	1.6 0	2.00

4. Conclusions

In this study we have reported the synthesis of sulfonylhydrazones and their complexes. The structural characterizations of synthesized compounds were made by using the elemental analyses, spectroscopic methods, magnetic susceptibility, thermal studies and conductivity measurements. It is concluded that sulfonylhydrazones act as a bidentate ligands, coordinating through >C=N and phenolic–OH via deprotonation. Based on physicochemical evidence, the proposed structure of arylsulfonylhydrazones and their complexes is exhibited in Fig. 2.

The biological activity screening shows that *5msalesh* has high inhibition effects against tested bacteria and CA II enzyme. Furthermore, our Ni(II) complexes have more inhibition effect than Co(II) complexes against CA II and tested bacteria.

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