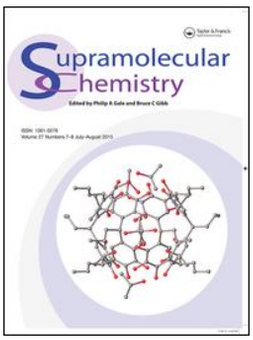


Supramolecular Chemistry

ISSN: 1061-0278 (Print) 1029-0478 (Online) Journal homepage: http://www.tandfonline.com/loi/gsch20

Benzoisothiazole-1,1-dioxide-based synthetic receptor for zinc ion recognition in aqueous medium and its interaction with nucleic acids

Milan Jakubek, Zdeněk Kejík, Veronika Antonyová, Robert Kaplánek, David Sýkora, Róbert Hromádka, Kateřina Vyhlídalová, Pavel Martásek & Vladimír Král

To cite this article: Milan Jakubek, Zdeněk Kejík, Veronika Antonyová, Robert Kaplánek, David Sýkora, Róbert Hromádka, Kateřina Vyhlídalová, Pavel Martásek & Vladimír Král (2018): Benzoisothiazole-1,1-dioxide-based synthetic receptor for zinc ion recognition in aqueous medium and its interaction with nucleic acids, Supramolecular Chemistry, DOI: 10.1080/10610278.2018.1523409

To link to this article: https://doi.org/10.1080/10610278.2018.1523409

Published online: 08 Oct 2018.

SUPRAMOLECULAR CHEMISTRY
https://doi.org/10.1080/10610278.2018.1523409

Taylor & Francis
Taylor & Francis Group

ARTICLE

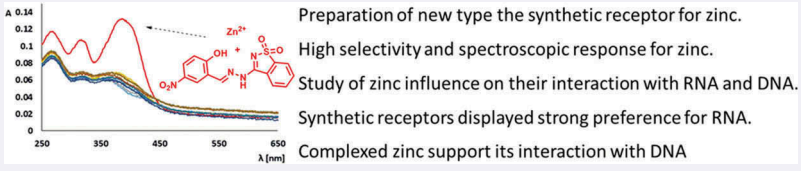
Benzoisothiazole-1,1-dioxide-based synthetic receptor for zinc ion recognition in aqueous medium and its interaction with nucleic acids

Milan Jakubek[a,b], Zdeněk Kejík[c], Veronika Antonyová[b], Robert Kaplánek[a,b], David Sýkora[a], Róbert Hromádka[b,d], Kateřina Vyhlídalová[a], Pavel Martásek[b,c] and Vladimír Král[a,b]

[a]Department of Analytical Chemistry, Faculty of Chemical Engineering, University of Chemistry and Technology, Prague, Czech Republic,; [b]BIOCEV, First Faculty of Medicine, Charles University, Czech Republic; [c]Department of Pediatrics and Adolescent Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague Ke Karlovu, Prague Czech Republic; [d]C2P s.r.o. Jungmannova 101, 503 51 Chlumec nad Cidlinou, Czech Republic

ABSTRACT

Benzoisothiazole-1,1-dioxide-based synthetic receptor was prepared by two step synthesis in 92 % overall yield. Its applicability for the determination of Zn(II) and interction with nucleic acids was studied by absorption spectroscopy. Obtained data, specifically low limit of detection, 0.15 μM (R^2 = 0.9933), showed the high potential of the tested structure motif for the recognition and determination of Zn(II) ions in aqueous media (water:DMSO; 99:1 (v/v)). Alone receptor displayed orderly strongly RNA affinity. Value of LogK was 6.1 and 4.9 for its complex (1:1) with RNA and DNA, respectively. Nevertheless, in presence of complexed Zn(II) ions, its DNA affinity (represent by K, LogK = 5.7) strongly grow to near value obtained for its interaction with RNA. On the other hand, its RNA affinity (LogK = 5.9) displayed not significantly change in the presence of complexed one.



ARTICLE HISTORY
Received 19 June 2018
Accepted 9 September 2018

KEYWORDS
Chelator; hydrazone; nucleic acid; zinc ions

1. Introduction

Recognition and determination of biologically important transition metals such as zinc is one of the major task of analytical and supramolecular chemistry. Zinc, or more precisely its divalent cation (Zn(II)) is the second most abundant transition metal and essential trace element in the living systems, for example the total amount of zinc in the adult body equals to 2–3 g (1, 2). Zn(II) participates in a number of biochemical and biological processes e.g., apoptosis, regulation of gene expression, neural signal transmission and many others. Zn(II) ion is also known as a cofactor of more than 300 proteins such as enzymes and DNA regulation factors (3). It is proved that zinc deficiency can lead to a number of serious pathological states such as retarded growth in children, brain disorders and high blood cholesterol. Moreover, neurodegenerative disorders such as Alzheimer's disease, epilepsy, ischemic stroke, and infantile diarrhoea are closely related to the imbalance in Zn(II) metabolism (4).

These facts stimulate the development of various analytical methods suitable for the determination of Zn(II) ions. Currently, sophisticated analytical techniques including inductively coupled plasma atomic emission or mass spectrometry and atomic absorption spectroscopy are extensively used for the determination of Zn(II) in environmental and biological samples (5–7). However, the mentioned approaches require a sophisticated instrumentation, high skill personnel and a tedious sample preparation. Therefore new alternative analytical tools such as selective synthetic receptors are intensely developed and studied. (8–18)

One promising structure building block for the construction of specific receptors for transition metals such as zinc is represented by benzoisothiazole-1,1-dioxide derivatives. Their ability to form complexes with transition metals was described by Fernanda *et al*. and Frija *et al*. (19, 20). Combination of benzoisothiazole-1,1-dioxide with selected structural motifs such as enamine nitrogen (from hydrazone) and phenolic hydroxy group possessing high affinity to transition metals could

CONTACT Milan Jakubek jakubek.milan@seznam.cz; VladimírKrálvladimir.kral@lf1.cuni.cz First Faculty of Medicine, Charles University, Průmyslová 595, Vestec 252 50, Czech Republic

provide promising way for the preparation of novel type of synthetic receptors for the determination of biological important metal ions such as Zn(II). It inspire us to prepare and evaluate a new benzoisothiazole receptor for the recognition and determination of Zn (II) ions in the aqueous environment. Because zinc complexes are perspective agents for the specific targeting and recognition of nucleic acids (21), interaction of synthetic receptor and its Zn(II) complexes with DNA and RNA was also observed in this study.

2. Experimental section

2.1. Materials and method

All chemicals, solvents and nucleic acid were purchased from Sigma–Aldrich (Czech Republic) and were used without further purification. Product number of used DNA (from salmon sperm) and RNA (from Torula utilis) were 31,149 and 83,850, respectively. UV–Vis absorption spectra were recorded using Varian Cary 400 SCAN UV–Vis Spectrophotometer (Varian, USA) where reference spectrum of a plain solvent was subtracted from all spectra of real samples. The NMR spectra were obtained with a Bruker Avance III 500 MHz (500 MHz for ^{1}H and 125 MHz for ^{13}C) (Bruker, Germany) at 25 °C in DMSO-d_6. The chemical shifts (δ) are presented in ppm (relative to TMS = 0.000 ppm) and the coupling constants (J) in Hz. Mass spectra were measured with a 3200 Q TRAP (AB Sciex, Canada) mass spectrometer fitted with an electrospray ion source. The analyte dissolved in methanol was introduced directly into the ESI source *via* a PEEK capillary at a flow rate of 10 µL/min. Nitrogen was used as a nebulizer gas. The operating conditions for the mass spectrometer were set as follows: ionspray voltage 5.5 kV; curtain gas 10, ion source gas(1) 18, and ion source gas(2) 0 psig; ion source temperature ambient; declustering potential 60 V, entrance potential 10 V.

2.2. Synthesis and characterisation of receptor 1

3-Hydrazinylbenzoisothiazole-1,1-dioxide (22) (138 mg; 0.7 mmol) and 2-hydroxy-5-nitrobenzaldehyde (167 mg; 1 mmol) were mixed in isopropanol (25 mL) and acetic acid (1 mL) was added. Reaction mixture was then stirred at 75 °C for 2 days. Then volatile compounds were evaporated under reduced pressure and residue was suspended in diethyl ether/petroleum ether mixture (1:1 v/v; 30 mL). Solid material was filtered, washed with additional portions of diethyl ether/petroleum ether mixture (1:1 v/v; 60 mL) and dried at 50 °C under vacuum. 2-{[2-(1,1-dioxidobenzoisothiazol-3-yl)hydraziny lidene]methyl}V-4-nitrophenol (synthetic receptor **1**) was obtained in the yield of 240 mg (92%) as yellowish solid.

^{1}H NMR (DMSO-d_6): δ 7.15 (7.18) (d, J = 9.1 Hz, 1H); 7.90 (m, 2H); 8.08 (m, 1H); 8.24 (m, 2H); 8.67 (8.59) (d, J = 2.9 Hz, 1H); 8.89 (8.63) (s, 1H); 12.11 (bs, 1H); 12.75 (bs, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 117.22 (117.03); 119.66 (120.24); 121.71 (122.34); 122.94; 123.34; 126.59; 127.64 (127.39); 133.37; 133.92 (134.24); 140.01 (140.06); 141.73 (143.24); 147.38 (144.88); 156.05 (158.82); 162.77 (162.34) ppm. . ESI-MS (m/z): 347 [M + H] + . Elem. Anal. Calcd. for $C_{14}H_{10}N_4O_5S$: C, 48.55; H, 2.91; N, 16.18. Found: C, 48.52; H, 2.90; N, 16.16.

2.3. Spectroscopic study of interaction of synthetic receptor 1 with metal ions

For UV-Vis 'on-off' study, 35 mg of synthetic receptor (**SR**) **1** was dissolved in DMSO to make concentration of 0.01 M in a 10 mL volumetric flask. 1 mL of the solution of **SR 1** was taken into a 1000 mL volumetric flask, and water was added to the total volume of 1000 mL in a volumetric flask. Final concentration of the **SR 1** in the stock solution was 10 µM.

Calculated amounts of the metal salts (nitrates) were dissolved in water/DMSO, 99:1, *v/v*, or above solution of **SR 1** in a 100 mL volumetric flask to make final concentration of the metal cation 10 µM.

UV-Vis spectra of the studied **SR 1** were measured in the presence and absence of the used cations. Data were collected in the range 220–900 nm with 1-nm data spacing in 1-cm quartz cell at scan rate 600 nm/min.

2.3.1. Determination of conditional binding constants and complex stoichiometry of SR 1 with zn (ii) ions

The association of **SR 1** with Zn(II) ions was studied using UV-Vis spectroscopy in aqueous solution (water/DMSO, 99:1, *v/v*). Because the solvent always significantly affects the binding constants, all titrations were performed at the same environment and the ratio of DMSO to water was hold constant. Conditional constants (Ks) were calculated from the absorbance changes ΔA of **SR 1** at the spectral maximum of their complexes with Zn(II) by nonlinear regression analysis with the Letagrop Spefo 2005 software. The computational model was described and discussed in detail elsewhere (23). To express of error of Ks was used standard deviation between measured and calculated absorption intensity (based on the determined K). Their values was defined as twice the values of these standard deviations.

The concentration of **SR 1** was 10 µM. The concentrations of Zn(II) varied in the range of 0–0.5 mM. UV-Vis

spectra were measured from 220 to 900 nm with 1-nm data spacing in 1-cm quartz cell at scan rate 600 nm/min.

2.3.2. Determination of detection limit of SR 1 for zn (ii) ions

The detection limit was determined from the titration data (24, 25) in aqueous solution (water/DMSO, 99:1, *v/v*). The values of the absorbance of **SR 1** at 385 nm (UV maximum of its zinc complexes) measured at various concentrations of Zn (II) were normalized taking into account the original absorbance at the absence of Zn (II) in the solution *versus* the final maximal absorbance (corresponding to the final addition of Zn(II)). A linear regression curve was then fitted to the normalized absorbance. The detection limits were calculated using the following equation: LOD = D/K, where D is the absolute value of the above curve for a zero concentration of Zn(II) and K is the slope of the dependence of the normalised absorbance $((A - A_{min})/(A_{max} - A_{min}))$ *vs*. Zn (II) concentration.

2.3.3. Study of interaction, determination of conditional binding constants and complex stoichiometry of synthetic receptor SR 1 and zinc complex of SR 1 with nucleic acids

1 mL DMSO solution of **SR 1** (0.01M) and 1ml water solution of Zn(II) ions (0.01 M) were stirring for 15 minutes together. Subsequently, 0.2 mL of the above prepared solution of zinc complex of **SR 1 (Zn-SR 1)** (0.005 M) was taken into a 100 mL volumetric flask, and 1mM HEPES buffer with calculated amount of DNA, or RNA adjusted on pH 7.34 ad was added to the total volume of 100 mL in a volumetric flask. Solution of alone **SR 1** was prepared in the same way, instead of the aqueous solution of zinc ions was used distilled water.

Because the DNA and RNA polymer chains have various lengths, the Ks values of **SR 1** and **Zn-SR 1** with DNA and RNA were calculated using the DNA and RNA concentration as defined by the concentration of each repeated base pair and base, respectively. Final concentration of **SR 1** and **Zn-SR 1** in the stock solution was 10 μM. The concentrations of DNA and RNA varied in the range of 0–0.1 mM. UV-Vis spectra were measured from 220 to 900 nm with 1-nm data spacing in 1-cm quartz cell at scan rate 300 nm/min.

The association of the **SR 1** and **Zn-SR 1** with DNA and RNA was studied using UV-Vis spectroscopy in 1mM HEPES buffer (water/DMSO, 99:1, v/v), pH = 7.4. Because the solvent always significantly affects the binding constants, all titrations were performed at the same environment and the ratio of DMSO to water was hold constant. Ks were calculated from the absorbance changes ΔA of **SR** 1, or **Zn-SR 1** with DNA, or RNA using the maximum of their complexes with DNA, or RNA by non-linear regression with the Letagrop Spefo 2005 software. To express of error of Ks was used standard deviation between measured and calculated absorption intensity (based on the determined K). Their values was defined as twice the values of these standard deviations.

3. Result and discussion

3.1. Chemistry

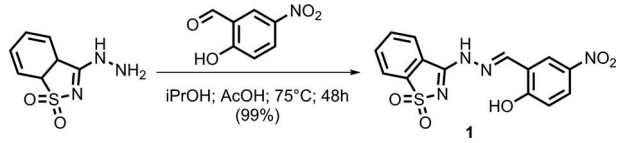
SR 1 was prepared by reaction of 3-hydrazinylbenzoisothiazole-1,1-dioxide (22) with excess of 2-hydroxy-5-nitrobenzaldehyde in isopropanol in the presence of acetic acid at 75 °C for 48 h in the yield of 99 % (Scheme 1).

3.1.1. Prototropic tautomerism

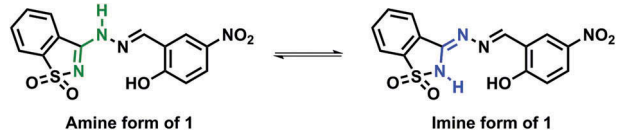
Heterocyclic hydrazones showed in some cases prototropic tautomerism – equilibrium between amino form (acidic proton is on the hydrazine nitrogen) and imino form (acidic proton is on the heterocyclic nitrogen) (Scheme 2). (22, 26) Prototropic tautomerism leads to two sets of signals in ^{1}H and ^{13}C NMR spectra. The ratio of tautomers is dependent on the pH and solvent; in the case of **SR 1** in DMSO-d_6, the ratio of tautomers calculated from the signals of the CH = N protons was 7:1. Ratio of tautomers was not significantly changed after addition of various amount of D_2O into DMSO-d_6 solution. Based on it, we can expected, than initial tautomer ratio in the water system (e.g. water/DMSO, 99:1, *v/v*), which was used for is approximately 7:1.

3.2. Uv-vis study of interaction of SR 1 with transition metals

Selectivity of the synthetic receptor for the recognition of Zn(II) ion was studied by UV-Vis absorption spectroscopy. This study was conducted in aqueous environment



Scheme 1. Preparation of **SR 1**.



Scheme 2. Prototropic tautomerism of **SR 1**.

(water/DMSO, 99:1, *v/v*) at 10 μM concentration of both, **SR 1** and appropriate metal cation. **SR 1** exhibited an absorption peak at 271 nm. Upon the addition of equimolar amount of Zn(II) into the solution of **SR 1** a significant change of the absorption such as appearance of new absorption peaks (λ_{max} = 322 and 385 nm) was observed (Figure 1). On the contrary, upon the addition of the other metal ions such as Co(II), Cu(II), Fe(III), Ni(II), Cd(II) Pb(II), Cr (III), Hg(II) Al(III), no or only slight spectra change was observed. It indicated, that **SR 1** prefer polarizable metal ions such as Zn(II). Fact, than was not observed interaction with Cu(II), which displayed similar properties with Zn(II) such as charge, average and polarizability could be explained geometry of created complex. It well known, that ligands with ability to form complex with tetrahedral geometry prefers Zn(II) ions other ions even Cu(II). (27)

In order to determine the applicability of **SR 1** for the determination of Zn(II) ions, the titration experiment was performed (Figure 2). Detailed titration curves are showed in Figure 2(c-d). In the presence of the added Zn(II) ions two new absorption peaks (λ_{max} = 322 and 385 nm) were observed. As the concentration of Zn(II) ion gradually increased the absorbance at the original spectral maximum at 271 nm and at the two new maxima strongly increased up to the concentration equal to 0.5 equivalents. Then the further additions of Zn(II) ions lead to the slow increase of the absorbance. Specifically, in the presence of 0.5 equivalent of Zn(II) ions the absorbance at 385 nm rised more than twice (from 0.05 to 0.12) with respect to the value at the absence of Zn (II). The highest value of absorbance (0.18) was observed when 296 Zn(II) equivalents were added into the studied solution. Ks of **SR 1** complex with zinc (II) ion were calculated by Letagrop Spefo 2005. Their value were $5.0x10^6 \pm 6\ x10^5$ and $1.3x10^{12} \pm 1.7x10^{11}$ for complex 1:1 and 1:2 (Zn(II) ions: receptor), respectively.

3.3. Determination of the detection limit and linear range of synthetic receptor 1 for zn(ii)

The detection limit of **SR 1** for Zn(II) was determined utilizing a plot of normalized absorbance *versus* the concentration of the Zn(II) present in the solution (24,

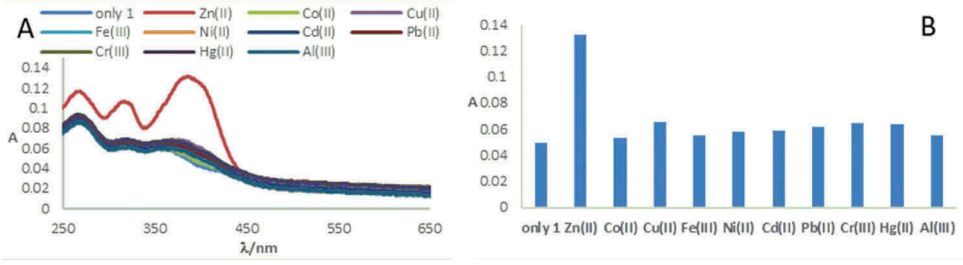


Figure 1. (Colour online) UV-Vis spectra (a) and absorbance (b) at 385 nm of **SR 1** (10 μM) with respect to the tested metal ions (10 μM) in aqueous medium (water/DMSO, 99:1, v/v).

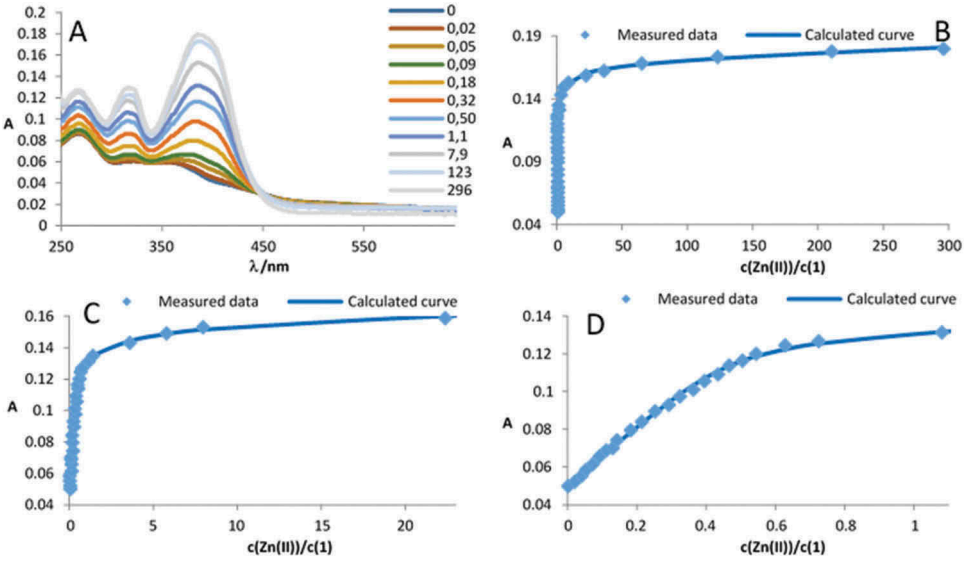


Figure 2. (Colour online) UV-Vis spectra of **SR 1** in the presence of zinc (II) ions (a) and titration curves (b, c and d) for SR **1** (10 μM), dependence of the complex absorbance at 385 nm on Zn(II) concentration in aqueous medium (water/DMSO, 99:1, v/v).

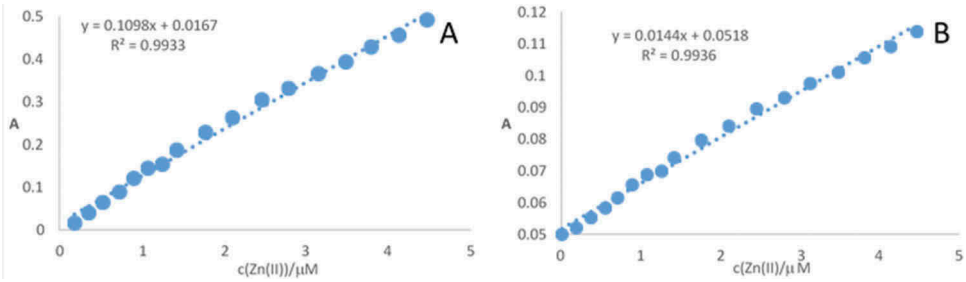


Figure 3. (Colour online) Limit of detection (a) and linear range (b) of **SR 1** (10 μM) at 385 nm for Zn(II) in aqueous medium (water/DMSO, 99:1, v/v).

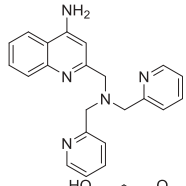
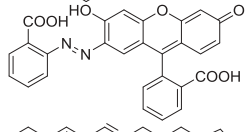
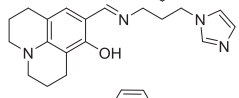
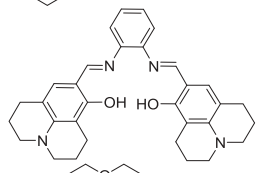
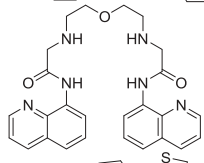
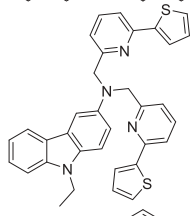
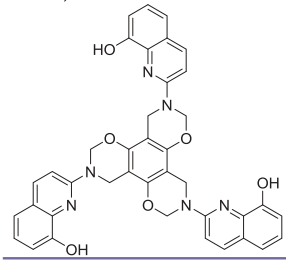
25). As shown in Figure 3, a linear relationship between the absorption intensity of studied **SR 1** in solution and the Zn(II) concentration was obtained. It was found that the prepared **SR 1** displayed very low limit of detection 0.15 μM. Linear range 0–4.5 μM implies its good potential for the determination of biologically relevant concentrations of Zn(II) ions. Average Zn(II) level found in the brain tissue is between 0.1–0.5 mM (4). Thus, we demonstrated that **SR 1** is highly sensitive to Zn(II) and it can be utilized to measure Zn(II) level in various analytical and bioanalytical applications.

The detection limit of the prepared synthetic receptor is comparable to other synthetic receptors for Zn(II) (Table 1). As can be seen, the values of the detection limits vary from 0.5 μM to 10 μM. It is well known that one of the main disadvantages of synthetic receptors stem in their limited usability in aqueous medium and the presence of a significant amount of organic co-solvent is necessary (Table 1). Organic additives suppress aggregation of the receptor and at the same time they improve the detection limits.

3.4. Study of the interaction mode using ^{1}H NMR

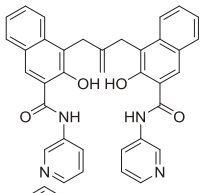
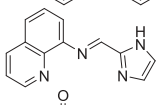
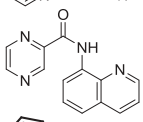
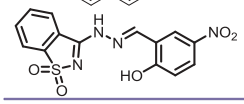
The ^{1}H NMR spectra of **SR 1** in the absence and presence of 1 equivalent of Zn(II) ions (as its nitrate salt) are shown in Figure 4. The results showed that the signals were shifted upon the addition of Zn(II) ions and the proton signals of the aromatic regions broadened and overlapped. The most significant changes upon the addition of Zn(II) ions occurred for the imine proton: δ 8.89 ppm was shifted downfield to δ 8.76 ppm (Figure 4). Similarly was observed, that signals arising from the other aromatic protons shift downfield by δ 0.05–0.15, except for the proton in the hydroxy group, which disappeared when the Zn(II) was complexed by **SR 1**. This results implied, that two N atom and one O atoms can participate on the complexation of Zn(II) by **SR 1**. On this base, we proposed that Zn(II) ion is bonded by phenolic oxygen, enamine nitrogen and heterocyclic nitrogen (O-N-N binding system od **SR 1**). Scheme 3 proposed the binding interaction of **SR 1** with Zn(II) ion. These results indicate the effective

Table 1. Various receptors described for the determination of Zn(II) ions.

Receptor	LOD [μM]	Medium (solvent ratio)	Ref.
	0.198	Acetonitrole/Tris–HCl buffer (9:1, v/v)	(8)
	1.2	Phosphate buffer/ Acetonitrile (3:1, v/v)	(9)
	1.56	Acetonitrile/HEPES buffer (9:1, v/v)	(10)
	10.9	DMF/Bis-Tris buffer (1:1, v/v)	(11)
	0.6	Bis-Tris buffer/ DMSO (99:1, v/v)	(12)
	3.7	HEPES buffer/ Acetonitrile (3:2, v/v)	(13)
	9.87	DMSO/HEPES buffer (4:1, v/v)	(14)

(*Continued*)

Table 1. (Continued).

Receptor	LOD [μM]	Medium (solvent ratio)	Ref.
	1	Acetonitrile/Water (4:1, v/v)	(15)
	5.81	Methanol/Water (4:1, v/v)	(16)
	1.11	Acetonitrile	(17)
	0.15	Water/DMSO (99:1, v/v)	This work

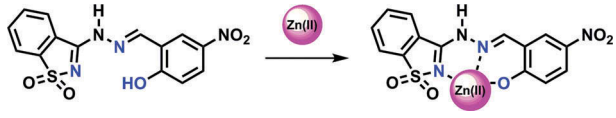
binding of Zn(II) ions by **SR 1**. Fourth ligand necessary for formation of tetrahedral complex is probably nitrate anion, or H_2O from used salt ($Zn(NO_3)_2.12H_2O$).

3.5 Interaction of zn-SR 1 and SR 1 with nucleic acids

Zn-SR 1 was generated *in situ* in the used medium. Its interaction with nucleic acid (DNA and RNA) was studied by absorption spectroscopy. As the concentration of DNA gradually increased absorbance of the original peak (λ_{max} = 385 nm) in UV spectrum significantly increased and it displayed moderate red shift to 390 nm up to 2 equivalents. For example, in the presence of 2 equivalents of DNA the absorbance at 390 nm raised approximately three times with relatively to the absorption in the absence of DNA in the system (from 0.11 to 0.28) (Figure 5). The above data are consistent with the expected binding of **Zn-SR 1** to the DNA. On the other hand alternatively explanation observed phenomena could be based on the dissociation of **Zn-SR 1** in the presence DNA and binding liberated **SR 1** to DNA.

Therefore confirmation of tested hypotheses, interaction of alone of **SR 1** with DNA was also studied (Figure 6). After DNA addition **SR 1** displayed also complex formation coupled with a significant improvement absorption (λ_{max} = 364 nm). Hover its position of maximum differed strongly from the maximum position (λ_{max} = 385 nm) found for the complex of **Zn-SR 1** with DNA. Differences in the shape and position of spectral peaks of **SR 1** and **Zn-SR 1** in the presence of nucleic acids indicated, that both of them can form complexes with DNA.

The interaction of **SR 1** and **Zn-SR 1** with RNA displayed similar pattern as the one obtained for the interaction with DNA (Figures 7 and 8). Positions of their absorption maxima were similar as in the previous case. Nevertheless the extent of the increase in absorbance observed for titration with RNA was significantly lower than in the case of DNA. On the other hand, values of Ks



Scheme 3. Proposed binding interaction of **SR 1** and Zn(II) yielded 1:1 complex

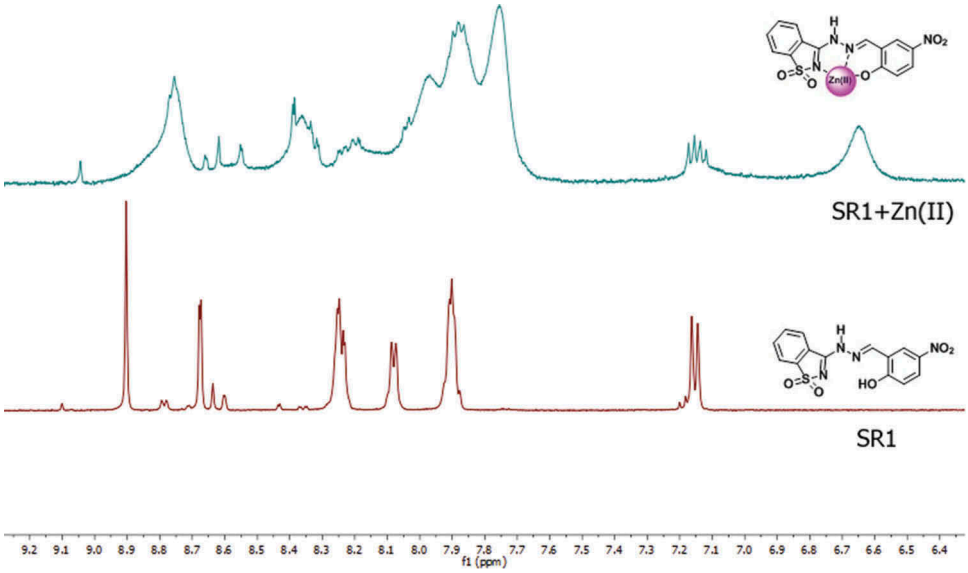


Figure 4. (Colour online) ^{1}H NMR spectra of **SR 1** upon addition of Zn(II) in DMSO-d_6.

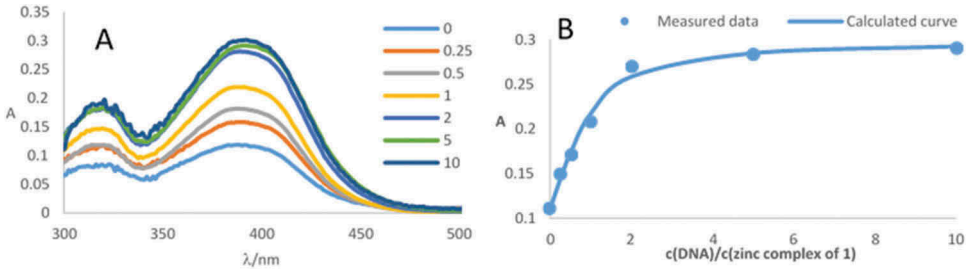


Figure 5. (Colour online) UV-Vis spectra of **Zn-SR 1** in the presence of DNA (a) and titration curve (b,) for **Zn-SR 1** (10 μM) dependence of the complex absorbance at 390 nm on DNA concentration in 1mM HEPES buffer (water/DMSO, 99:1, v/v), pH = 7.34.

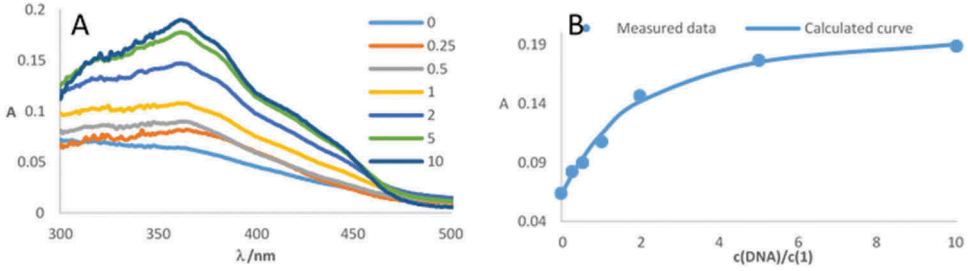


Figure 6. (Colour online) UV-Vis spectra of **SR 1** in the presence of DNA (a) and titration curve (b,) for **SR 1** (10 μM) dependence of the complex absorbance at 364 nm on DNA concentration in 1mM HEPES buffer (water/DMSO, 99:1, v/v), pH = 7.34.

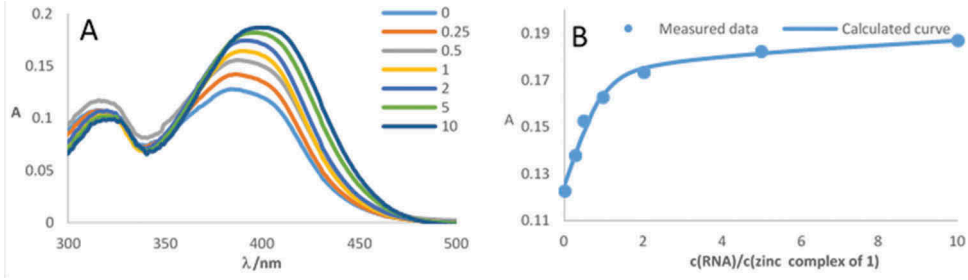


Figure 7. (Colour online) UV-Vis spectra of **Zn-SR 1**in the presence of RNA (a) and titration curve (b,) for **Zn-SR 1** (10 μM) dependence of the complex absorbance at 390 nm on RNA concentration in 1mM HEPES buffer (water/DMSO, 99:1, v/v), pH = 7.34.

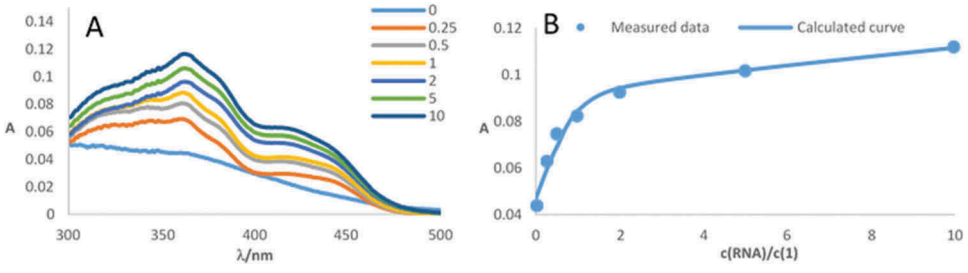


Figure 8. (Colour online) UV-Vis spectra of **SR 1** in the presence of RNA (a) and titration curve (b,) for **SR 1** (10 μM) dependence of the complex absorbance at 364 nm on RNA concentration in 1mM HEPES buffer (water/DMSO, 99:1, v/v), pH = 7.34.

of **SR 1** and **Zn-SR 1** with DNA were not significantly higher than for their complexes with RNA (you seen in Table 2), stoichiometry of observed complexes was 1:1.

Alone **SR 1** displayed significantly higher affinity for the RNA against DNA, while **Zn-SR 1** don't show significantly RNA preference. It is well known, that DNA have twice the number of binding sites (e.g. bases) than RNA. Based on this, one can expect that these receptors should be higher preference for the DNA. On the other hand, unlike DNA, RNA bases are

Table 2. The Ks of **Zn-SR 1** and **SR 1** with DNA and RNA.

Nucleic acid	DNA	RNA
Receptor	Log *Ks*	Log *Ks*
Zn-SR 1	5.7 ± 0.23	5.9 ± 0.28
SR 1	4.9 ± 0.17	6.1 ± 0.15

[a]Stoichiometry of complexes was 1:1.

not bound by complementary bases via hydrogen bond and therefore they can be more accessible for interaction. Fact that both tested receptors prefers RNA suggests, they interact with nucleobases via hydrogen bond, or other non-covalent interaction. It is implied, that not only **SR 1**, but also metal complexes such as **Zn-SR 1** can represent perspective structure motif for the recognition and targeting nucleic acids.

4. Conclusions

In the present work the novel type of zinc receptor based on benzoisothiazole-1,1-dioxide structure motif was synthesized and studied. Its chemical structure was characterised by NMR and MS. Its binding ability was evaluated with absorption spectroscopy. The prepared **SR 1** exhibited selective spectroscopic response for Zn(II) ion in aqueous medium with low detection limit of 0.15 μM. Thus, it indicated a its high potential for sensitive detection of Zn(II) ion in the aqueous environment. In addition, **SR 1** and **Zn-SR 1** represent of promising structure motif for the recognition of nucleic acids.

Acknowledgments

This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic within the National Sustainability Program II [Project BIOCEV-FAR, LQ1604] and by the project "BIOCEV" [CZ.1.05/1.1.00/02.0109]; the Technology Agency of the Czech Republic [project TE01020028]; Charles University in Prague [UNCE 204011/2012 and PRVOUK P24/LF1/3]. This work was also supported by the "Operational Programme Prague – Competitiveness" (CZ.2.16/3.1.00/21537) and the "National Programme of Sustainability I" - NPU I (LO1601 - No.: MSMT-43760/2015). Besides, we also thank for the financial support of this work the Ministry of Education, Youth and Sports of the Czech Republic grant no. LM201564 (EATRIS-CZ). This work was also supported by Ministry of Agriculture of Czech republic [QJ1610515] and Ministry of Industry and Trade [FV20572].

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Technology Agency of the Czech Republic [project TE01020028]; Operational Programme Prague – Competitiveness [CZ.2.16/3.1.00/21537]; Ministry of Education, Youth and Sports of the Czech Republic [BIOCEV-FAR, CZ.1.05/1.1.00/02.0109, LM201564, LQ1604] and National Programme of Sustainability [MSMT-43760/2015]; Charles University in Prague [PRVOUK P24/LF1/3, UNCE 204011/2012]; Ministry of Agriculture of Czech Republic (QJ1610515)

ORCID

Pavel Martásek http://orcid.org/0000-0001-6165-4444

References

(1) Ricachenevsky, F.K.; Menguer, P.K.; Sperotto, R.A.; Fett, J. P. Got to Hide Your Zn Away: Molecular Control of Zn Accumulation and Biotechnological Applications. *Plant Sci*. **2015**, *236*, 1–17. DOI:10.1016/j.plantsci.2015.03.009

(2) Jiang, P.J.; Guo, Z.J. Fluorescent Detection of Zinc in Biological Systems: Recent Development on the Design of Chemosensors and Biosensors. *Coordin. Chem. Rev*. **2004**, *248*, no. 1–2, 205–229. DOI:10.1016/j.cct.2003.10.013

(3) Palmgren, M.G.; Clemens, S.; Williams, L.E.; Kraemer, U.; Borg, S.; Schjorring, J.K.; Sanders, D. Zinc Biofortification of Cereals: Problems and Solutions. *Trends Plant Sci*. **2008**, *13*, no. 9, 464–473. DOI:10.1016/j.tplants.2008.06.005

(4) Bush, A.I.;. Metals and Neuroscience. *Curr. Opin. Chem. Biol*. **2000**, *4*, no. 2, 184–191.

(5) Rajabi Khorrami, A.; Fakhari, A.R.; Shamsipur, M.; Naeimi, H. Pre-Concentration of Ultra Trace Amounts of Copper, Zinc, Cobalt and Nickel in Environmental Water Samples Using Modified C18 Extraction Disks and Determination by Inductively Coupled Plasma–Optical Emission Spectrometry. *Int. J. Environ. Anal. Chem*. **2009**, *89*, no. 5, 319–329. DOI:10.1080/03067310802549953

(6) Ghaedi, M.; Ahmadi, F.; Shokrollahi, A. Simultaneous Preconcentration and Determination of Copper, Nickel, Cobalt and Lead Ions Content by Flame Atomic Absorption Spectrometry. *J. Hazard. Mater*. **2007**, *142*, no. 1–2, 272–278. DOI:10.1016/j.jhazmat.2006.08.012

(7) Rao, K.S.; Balaji, T.; Rao, T.P.; Babu, Y.; Naidu, G.R.K. Determination of Iron, Cobalt, Nickel, Manganese, Zinc, Copper, Cadmium and Lead in Human Hair by Inductively Coupled Plasma-Atomic Emission Spectrometry. *Spectrochim. Acta B*. **2002**, *57*, no. 8, 1333–1338. DOI:10.1016/S0584-8547(02)00045-9

(8) Gao, C.J.; Jin, X.J.; Yan, X.H.; An, P.; Zhang, Y.; Liu, L.L.; Tian, H.; Liu, W.S.; Yao, X.J.; Tang, Y. A Small Molecular Fluorescent Sensor for Highly Selectivity of Zinc Ion. *Sensor Actuat. B Chem*. **2013**, *176*, 775–781. DOI:10.1016/j.snb.2012.09.052

(9) Chantalakana, K.; Choengchan, N.; Yingyuad, P.; Thongyoo, P. A Highly Selective 'Turn-On' Fluorescent Sensor for Zn2+ Based on Fluorescein Conjugates. *Tetrahedron Lett*. **2016**, *57*, no. 10, 1146–1149. DOI:10.1016/j.tetlet.2016.01.106

(10) Choi, Y.W.; Park, G.J.; Na, Y.J.; Jo, H.Y.; Lee, S.A.; You, G.R.; Kim, C. A Single Schiff Base Molecule for Recognizing Multiple Metal Ions: A Fluorescence Sensor for Zn(II) and Al(III) and Colorimetric Sensor for Fe(II) and Fe(III). *Sensor Actuat. B Chem*. **2014**, *194*, 343–352. DOI:10.1016/j.snb.2013.12.114

(11) Choi, Y.W.; You, G.R.; Lee, J.J.; Kim, C. Turn-On Fluorescent Chemosensor for Selective Detection of Zn2+ in an Aqueous Solution: Experimental and Theoretical Studies. *Inorg. Chem. Commun*. **2016**, *63*, 35–38. DOI:10.1016/j.inoche.2015.11.012

(12) Jung, J.M.; Lee, S.Y.; Nam, E.; Lim, M.H.; Kim, C. A Highly Selective Turn-On Chemosensor for Zn2+ in Aqueous Media and Living Cells. *Sensor Actuat. B Chem*. **2017**, *244*, 1045–1053. DOI:10.1016/j.snb.2017.01.076

(13) Mahapatra, A.K.; Maji, R.; Maiti, K.; Mondal, S.; Ali, S.S.; Manna, S.K.; Sahoo, P. Carbazole-Driven Ratiometric Fluorescence Turn on for Dual Ion Recognition of Zn2+ and Hg2+ by Thiophene-Pyridyl Conjugate in HEPES Buffer Medium: Spectroscopy, Computational, Microscopy and Cellular Studies. *Supramol. Chem*. **2017**, *29*, no. 3, 215–228. DOI:10.1080/10610278.2016.1202412

(14) Mahapatra, A.K.; Manna, S.K.; Das Mukhopadhyay, C.; Mandal, D. Pyrophosphate-Selective Fluorescent Chemosensor Based on Ratiometric tripodal-Zn(II) Complex: Application in Logic Gates and Living Cells. *Sensor Actuat. B Chem*. **2014**, *200*, 123–131. DOI:10.1016/j.snb.2014.04.034

(15) Mehdi, H.; Pang, H.C.; Gong, W.T.; Wajahat, A.; Manivannan, K.D.; Shah, S.; Ye, J.W.; Ning, G.L. Two New Fluorescent Zn2 + Sensors Exhibiting Different Sensing Mode with Subtle Structural Changes. *Supramol. Chem*. **2017**, *29*, no. 5, 378–386. DOI:10.1080/10610278.2016.1242730

(16) Mukherjee, S.; Talukder, S. A Reversible Luminescent Quinoline Based Chemosensor for Recognition of Zn2 + Ions in Aqueous Methanol Medium and Its Logic Gate Behavior. *J. Lumin*. **2016**, *177*, 40–47. DOI:10.1016/j.jlumin.2016.04.016

(17) Sohrabi, M.; Amirnasr, M.; Farrokhpour, H.; Meghdadi, S. A Single Chemosensor with Combined Ionophore/Fluorophore Moieties Acting as A Fluorescent "Off-On" Zn 2+ Sensor and A Colorimetric Sensor for Cu 2+: Experimental, Logic Gate Behavior and TD-DFT Calculations. *Sensors Actuators B Chem*. **2017**, *250*, 647–658. DOI:10.1016/j.snb.2017.05.015

(18) Carter, K.P.; Young, A.M.; Palmer, A.E. Fluorescent Sensors for Measuring Metal Ions in Living Systems. *Chem. Rev*. **2014**, *114*, no. 8, 4564–4601. DOI:10.1021/cr400546e

(19) Fernanda, M.; Carvalho, N.N.; Consiglieri, A.C.; Duarte, M.T.; Galvao, A.M.; Pombeiro, A.J.L.; Herrmann, R. Transition-Metal Complexes of (1s,2s,3r)-3-Hydroxycamphorsultam. *Inorg. Chem*. **1993**, *32*, no. 23, 5160–5164. DOI:10.1021/ic00075a036

(20) Frija, L.M.T.; Fausto, R.; Loureiro, R.M.S.; Cristiano, M.L.S. Synthesis and Structure of Novel Benzisothiazole-Tetrazolyl Derivatives for Potential Application as Nitrogen Ligands. *J. Mol. Cata. a-Chem*. **2009**, *305*, no. 1–2, 142–146. DOI:10.1016/j.molcata.2008.12.007

(21) Terenzi, A.; Lauria, A.; Almerico, A.M.; Barone, G. Zinc Complexes as Fluorescent Chemosensors for Nucleic Acids: New Perspectives for a "Boring" Element. *Dalton T*. **2015**, *44*, no. 8, 3527–3535. DOI:10.1039/C4DT02881C

(22) Kejik, Z.; Kaplanek, R.; Havlik, M.; Briza, T.; Vavrinova, D.; Dolensky, B.; Martasek, P.; Kral, V. Aluminium(III) Sensing by Pyridoxal Hydrazone Utilising the Chelation Enhanced Fluorescence Effect. *J. Lumin*. **2016**, *180*, 269–277. DOI:10.1016/j.jlumin.2016.08.047

(23) Brito, F.; Ingri, N.; Sillen, L.G., are Aqueous Metavanadate Species Trinuclear Tetranuclear or Both - Preliminary Letagrop Recalculation of Emf Data. *Acta Chem. Scand*. **1964**, *18*, no. 6, 1557-&. DOI:10.3891/acta.chem.scand.18-1557

(24) Jakubek, M.; Kejik, Z.; Parchansky, V.; Kaplanek, R.; Vasina, L.; Martasek, P.; Kral, V. Water Soluble Chromone Schiff Base Derivatives as Fluorescence Receptor for aluminium(III). *Supramol. Chem*. **2017**, *29*, no. 1, 1–7. DOI:10.1080/10610278.2016.1153095

(25) Jakubek, M.; Kejik, Z.; Kaplanek, R.; Vesela, H.; Sykora, D.; Martasek, P.; Kral, V. Perimidine-Based Synthetic Receptors for Determination of copper(II) in Water Solution. *Supramol. Chem*. **2018**, *30*, no. 3, 218–226. DOI:10.1080/10610278.2017.1414216

(26) D'Acunto, C.W.; Kaplanek, R.; Gbelcova, H.; Kejik, Z.; Briza, T.; Vasina, L.; Havlik, M.; Ruml, T.; Kral, V. Metallomics for Alzheimer's Disease Treatment: Use of New Generation of Chelators Combining Metal-Cation Binding and Transport Properties. *Eur. J. Med. Chem*. **2018**, *150*, 140–155. DOI:10.1016/j.ejmech.2018.02.084

(27) Haas, K.L.; Franz, K.J. Application of Metal Coordination Chemistry to Explore and Manipulate Cell Biology. *Chem. Rev*. **2009**, *109*, no. 10, 4921–4960. DOI:10.1021/cr900134a