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Metal complexes of benzimidazole derived sulfonamide: Synthesis, molecular structures and antimicrobial activity

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ABSTRACT

Benzimidazole and sulfonamide moieties are found in a number of pharmaceutically active molecules. By incorporating the sulfonamide pharmacophore into the benzimidazole scaffold, we prepared 2-(*o*-sulfamoylphenyl)benzimidazole **1** from saccharin as a precursor. Ligand **1** was coordinated to the divalent transition metals Mn(II) **2**, Co(II) **3**, Ni(II) **4**, Cu(II) **5** and Zn(II) **6** to yield complexes of the general formula $[ML_2(H_2O)_n]$ ($n = 2$ for **2** and $n = 0$ for **3**–**6**). All the compounds were characterized by elemental analysis, conductivity measurements, magnetic susceptibility, FT-IR and NMR spectroscopy. The molecular structures of **1**, **3** and **6** were determined by X-ray diffraction analysis. In all metal complexes, **1** behaved as a bidentate chelating ligand through the sulfonamidate nitrogen and the endocyclic nitrogen of benzimidazole. The molecular structures of **3** and **6** showed tetrahedral geometry around the Co(II) and Zn(II) centers, respectively. The molar conductivity data revealed the metal complexes to be non-electrolytes. The benzenesulfonamide derivative and its metal complexes were evaluated for their potential antimicrobial activity against a range of bacterial and fungal strains. [Co(2-(*o*-sulfamoylphenyl)benzimidazolate)$_2$] **3** was identified as the most active antibacterial compound, while none of the compounds exhibited antifungal activity.

1. Introduction

The aromatic and heterocyclic sulfonamides constitute an important class of bioactive small molecules. Some examples of clinically used sulfonamide-based drugs are acetazolamide, methazolamide, ethoxzolamide, and benzolamide (Fig. 1). These are widely used in clinics for example as antiglaucoma agents, antiepileptic, diuretic and antiobesity drugs [1–4]. In recent years, they have been extensively investigated as inhibitors of carbonic anhydrases (CAs, EC 4.2.1.1), which is one of the most important zinc–containing metalloenzymes involved in several physiological processes [5]. Sulfonamides (RSO_2NH_2) proved to be excellent inhibitors of CAs. Mechanistic studies on more than 200 CA X-ray crystal structures with inhibitors showed that sulfonamidates (RSO_2NH^-) bind to the zinc ion of the enzyme active site and disrupt the catalytic process. The remaining scaffold of the drug molecule participates in multiple interactions with amino acid residues and water molecules, which further stabilize the enzyme–inhibitor adduct [5–7].

Metal-based drugs are widely employed for the treatment and diagnosis of a range of diseases [8–12]. For example, complexes of platinum are used as anticancer, of gold as anti-arthritic and silver compounds as antimicrobial agents, whereas gadolinium and manganese derivatives play an important role as MRI contrast agents [13]. This led several research groups to prepare metal complexes of clinically-used heterocyclic sulfonamides and they were evaluated for their biological properties [4,5,7,14]. Sulfonamides turned out to be versatile ligands and form interesting coordination complexes under basic conditions in alcoholic solutions with

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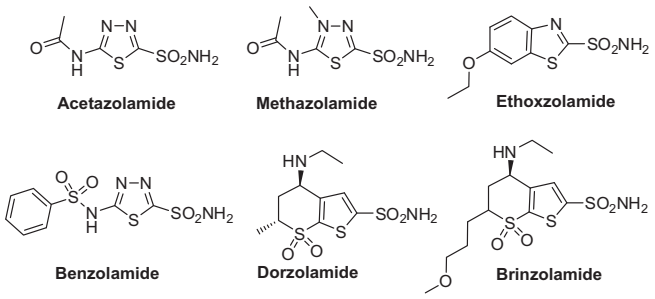


Fig. 1. The structures of lead sulfonamides used in clinics.

a wide range of transition metal ions. For example, acetazolamide formed coordination complexes with metal ions such as Ag(I), Co(II), Ni(II), Cu(II) and Zn(II) [15–17]. In all these compounds, the anionic acetazolamide coordinated through the sulfonamidate nitrogen and the endocyclic nitrogen atom and acted as a mono-, bi- or tridentate ligand [17]. Surprisingly, several of these metal complexes were 10–100 times stronger CA inhibitors than acetazolamide *per se*. This unexpected activity was explained by a dual mechanism of action. Under the conditions used in the enzyme inhibition assay, the metal complexes partially dissociate into the ligand and metal ion and both these entities interact separately with different areas of the active site of the enzyme [5,7].

The benzimidazole core is another privileged substructure present in a number of biomolecules including the purine bases of DNA and vitamin B_{12} as well as in a range of therapeutic agents [18]. This versatile heterocyclic scaffold is also found in potent antimicrobial, anti-HIV, antioxidant and antitumor agents [19–22]. The metal complexes of benzimidazole and its derivatives have been evaluated for medicinal applications such as anticancer agents, antioxidant and enzyme inhibitors [8,23–26].

In this paper, we report the preparation of a hybrid ligand system featuring both sulfonamide and benzimidazole pharmacophores. This hybrid benzimidazole-based sulfonamide derivative was used to prepare metal complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) and the antimicrobial activity of these compounds was tested.

2. Results and discussion

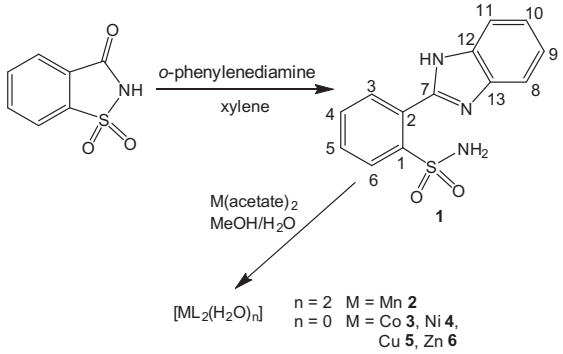
2.1. Synthesis and characterization

To combine benzimidazole and sulfonamide functionalities in a single molecule, a one pot synthesis was used to prepare **1**. The cheap and commercially available precursor saccharin, *i.e.*, 1,2-benzisothiazol-3-one-1,1-dioxide, a cyclic secondary sulfonamide widely used as calorie-free substitute of sugar for many years [27], has remarkable activity and selectivity profile towards inhibition of carbonic anhydrase IX compared to all other CA isozymes [28,29]. Saccharin was refluxed with *o*-phenylenediamine in xylene for 4 h to obtain **1** (Scheme 1), which was recrystallized from methanol for purification. Two equivalents of **1** were then reacted with the divalent transition metal ions Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) in methanol/water (Scheme 1). The formed metal complexes were air stable with high melting points and were insoluble in water and methanol, but soluble in DMF and DMSO. The ligand and its metal complexes were characterized by elemental analysis, FT-IR and NMR spectroscopy, conductivity and magnetic measurements, as well as single crystal X-ray crystallographic studies.

In the vibrational spectrum of **1**, three sharp N–H peaks with different intensities were present. One was assigned to the imidazole and two to the sulfonamide group while only one peak was found in the spectra of the Zn(II) and Ni(II) complexes or two weak signals of equal intensities in the spectra of the Mn(II), Co(II), and Cu(II) complexes. The stretching frequency of the remaining N–H of sulfonamide was shifted to lower wavenumbers. A similar trend was observed in case of bending vibrations where the N–H deformations merge with the bending vibrations of aromatic C–H groups. In case of **1**, the three N–H bending vibrations give a single peak at 1554 cm^{-1} which shifted to the range 1448–1431 cm^{-1} in the metal complexes and merged with peaks assigned to C–H aromatic deformations to gave a relatively broad and more intense peak in complexes compared to unbound sulfonamide.

The benzimidazole motif gave a peak at 1610 cm^{-1} assignable to the $\nu_{C=N}$ of the imidazole ring. This stretching frequency was shifted to lower wavenumbers in the range 1562–1531 cm^{-1} upon coordination of the imine nitrogen to the metal ions. Upon coordination of the nitrogen of the sulfonamide group to the metal center, a decrease in wavenumber of 23–56 cm^{-1} in the asymmetric stretching frequency of the sulfonyl group was observed [30]. In case of the Mn(II) complex **2**, the spectrum showed a broad band around 3500–3400 cm^{-1}, attributable to the presence of coordinated water.

The ^{1}H NMR spectrum of **1** showed the typical splitting pattern for aromatic protons of benzenesulfonamide, giving two dd at δ = 8.11 and 7.89 ppm for H3 and H6, while the signals for H4 and H5 appeared as two dt at δ = 7.82 and 7.74 ppm, respectively. The aromatic protons of benzimidazole appeared as four doublets, with overlapping of signals for H8 and H11 as well as for H9 and H10 (Fig. 2). The NH protons of imidazole and sulfonamide were not observed in d_6-DMSO probably due to fast proton exchange. The ^{1}H NMR spectra of Ni(II) and Zn(II) complexes contained the characteristic signals for the aromatic protons of the ligand, while



Scheme 1. Synthetic route for the preparation of the benzimidazole-derived phenylsulfonamide **1** (with NMR numbering scheme) and its metal complexes.

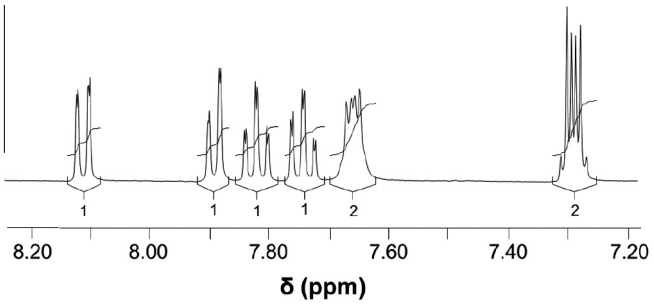


Fig. 2. ^{1}H NMR spectrum of **1**, showing the multiplicity of the aromatic protons.