

## Review

## Coordination chemistry of thiazoles, isothiazoles and thiadiazoles



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## ABSTRACT

Thiazole derived compounds have great potential in medicinal- and agro-chemistries, catalysis, cosmetic industry, corrosion protection, light harvesting, production of light-emitting diodes (LEDs), photochromes and molecular switches or nonlinear optical materials. In spite of that, not much attention has been paid to the coordination chemistry of this class of versatile and polyfunctional heterocyclic ligands. This review intends to systematize the existing information in this field and to highlight some perspectives in the synthesis and applications of 1,3-thiazole, isothiazole and thiadiazole metal complexes.

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## 1. Introduction

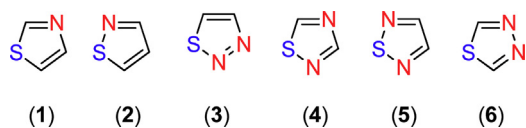
Multidonor heterocyclic ligands containing both nitrogen and sulfur atoms possess versatile coordination ability toward various transition metal ions; as a result, they have attracted considerable interest, particularly in the synthesis and applications of biomimicking and bioactive coordination compounds [1–3]. Among the ligands of this kind, electron-rich polyfunctional thiazole, isothiazole and thiadiazole-based derivatives assume an exceptional importance on the construction of metal complexes of different types, in particular valuable organometallic frameworks and functional materials. Accordingly, this review aims to systematize the current information in this field and provide some perspectives for possible applications of this important class of coordination compounds.

Generally, the thiazole heterocycle can adopt two isomeric forms (Fig. 1), i.e., 1,3-thiazole (**1**, often qualified as thiazole) or 1,2-thiazole (**2**, also recognized as isothiazole) in which the heteroatoms are in adjacent positions. Likeminded, the thiadiazole ring can assume four distinct isomers (**3–6**, Fig. 1). Nevertheless, derivatives of 1,3,4-thiadiazole (**6**, Fig. 1) are frequently applied as ligands in coordination chemistry; thus, this particular isomer will be mainly considered in this review and referred to as just thiadiazole if not otherwise mentioned.

Thiazoles and their derivatives are abundant in natural products, biologically active alkaloids and some pharmaceuticals. Trisubstituted and disubstituted 1,3-thiazoles, mainly linked to aryl or heteroaryl groups, are privileged structural motifs and have applications in different fields, such as materials science on the preparation of liquid crystals [4], molecular switches [5], sensors [6] or cosmetic industry (sunscreens) [7]. In addition, they have also been used in medicinal chemistry to access bioactive lead molecules and drug candidates. Some di- and trisubstituted 1,3-thiazole derivatives with their pharmacological properties are shown in Fig. 2 [8,9]. Apart from that, thiazole in the form of

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**Fig. 1.** Unsubstituted 1,3-thiazole (1), 1,2-thiazole (isothiazole) (2), 1,2,3-thiadiazole (3), 1,2,4-thiadiazole (4), 1,2,5-thiadiazole (5) and 1,3,4-thiadiazole (6).

thiazolium ion is a well-known organocatalyst in several C–C bond forming reactions [10]. Besides, photochemical isomerization of thiazoles is very important for many applications and has been studied recently in detail [11].

1,2-Thiazole (isothiazole) was first synthesized in 1956 [12]. Subsequently, a rapid progress in isothiazole chemistry was achieved. Intense studies onto the synthesis and chemical transformations of its derivatives were carried out in the last three decades of 20th century, initiated mainly by the extraordinarily broad range of useful properties showed by several compounds of this class of heterocycles. For instance, isothiazole-containing penicillins and cephalosporins competed successfully with ampicillin in their activities against gram-positive and Gram-negative bacteria. Moreover, some isothiazole derivatives were efficient in the treatment of Alzheimer disease, as anti-inflammatory, antithrombotic and anticonvulsive drugs and serine protease inhibitors (Fig. 3). Molecular constructs containing isothiazole have been used in color photography for stabilization of photo-materials, as protectors for polymers, dyes, detergents and leather goods or in waste decontamination [13].

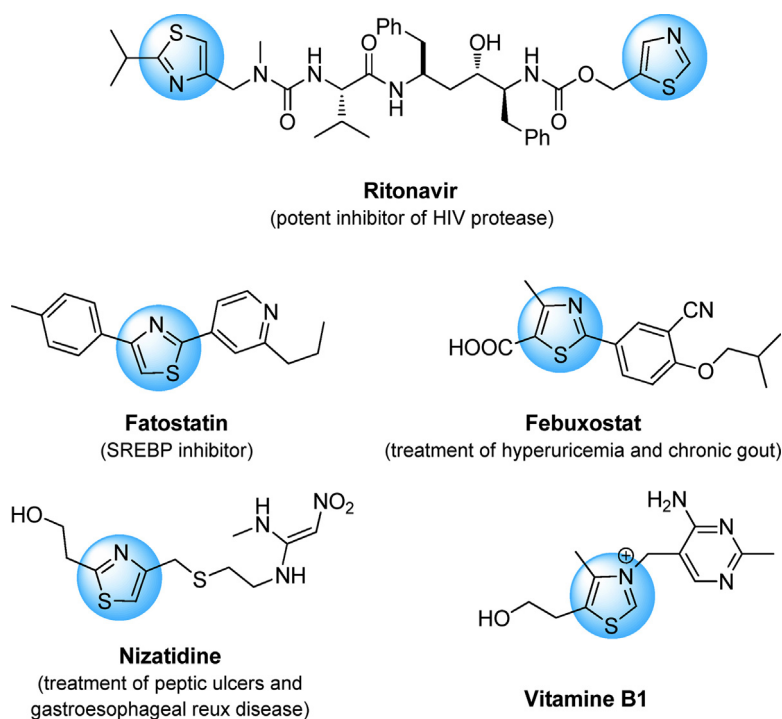
The syntheses and transformations of isothiazoles have been documented in several reviews [12,14] and books [15] where isothiazoles are considered in conjunction with other heterocyclic compounds. Moreover, to our knowledge, only one relevant review was written focusing the use of saccharin derivatives (a particular class of isothiazoles) as ligands upon the creation of organometallic structures [16]. In this review the authors performed an overview of metal complexes of saccharinate anion, obtained by deprotonation of the N–H moiety of saccharin (1,2-benzisothiazole-3(2H)-one

1,1-dioxide), one of the best known isothiazole derivatives and most widely used artificial sweetening agents. A wide variety of metal species based on mononuclear, oligonuclear complexes and extended coordination polymers were discussed in relation to the coordination modes of the anion, *i.e.*, monodentate (through the N-atom or the carbonylic O-atom), bidentate, tridentate or bridge forming. A brief overview on metallic complexes of thiosaccharin was also exposed by the authors. In view of this review, here we will not address derivatives of saccharin as ligands.

Other representatives of this homological family of heterocycles, namely thiadiazoles, are key structural elements for many pharmaceutical and chemical applications. For instance, diverse 1,2,5-thiadiazoles have been tested as starting materials to give narrow-bandgap polymers with interesting physical properties such as intrinsic conductivities and good nonlinear optical properties [17]. In turn, 1,2,3-thiadiazoles are widely applied in agrochemistry [18], while several 1,2,4-thiadiazole derivatives were identified as potent, selective and orally active cyclooxygenase-2 inhibitors [19].

Among the thiadiazole isomers, 1,3,4-thiadiazoles are especially prominent in terms of applications. Thus, derivatives of these heterocycles display a broad spectrum of biological activities comprising anticancer, antimicrobial, antituberculosis, anti-inflammatory, antidepressant and antihypertensive, among others. One of the most eminent thiadiazole containing compounds is acetazolamide (also known under the trade name Diamox), the famous carbonic anhydrase inhibitor used in treatment of glaucoma, high-altitude illness, idiopathic intracranial hypertension, hemiplegic migraine, obstructive sleep apnea, congenital myasthenic syndromes, *etc.* [20].

1,3,4-Thiadiazoles also exhibit high potential in agrochemistry as herbicides, fungicides, insecticides, bactericides, and plant-growth regulators. Besides, due to the 1,3,4-thiadiazole core's electron-deficient nature and good electron-accepting ability as well as thermal and chemical stability, thiadiazoles are widely applied in optics and electrochemistry. In addition, other applications are provisioned, which exploit their charge-transporting



**Fig. 2.** Illustrative examples of bioactive substituted 1,3-thiazoles.

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