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Review

Importance of Biometals as Targets in Medicinal Chemistry: An Overview about the Role of Zinc (II) Chelating Agents

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Abstract: Zinc (II) is an important biometal in human physiology. Moreover, in the last two decades, it was deeply studied for its involvement in several pathological states. In particular, the regulation of its concentration in synaptic clefts can be fundamental for the treatment of neurodegenerative diseases, such as Alzheimer's disease (AD). Zinc (II) is also a constituent of metalloenzymes (i.e., matrix metalloproteinases, MMPs, and carbonic anhydrases, CAs) with catalytic function; therefore, it can be an important target for the inhibition of these proteins, frequently involved in cancer onset. This review is focused on the significance of zinc (II) chelating agents in past and future medicinal chemistry research, and on the importance of selectivity in order to revamp the possibility of their use in therapy, often hindered by possible side effects.

Keywords: biometals; zinc; Alzheimer's disease; Matrix Metalloproteinase inhibitors; carbonic anhydrase; chelation therapy

1. Introduction

Several metal ions play an important role in many biological processes, and, of course, in human physiology and their assumption through diet is important for our health, with the difference in amounts and qualities according to the age [1]. However, it is important the difference between nonessential and essential metals. Arsenic, cadmium, lead, and mercury are ubiquitous but do not play biochemical roles in humans. Furthermore, they are toxic and act in tissues by inducing several dangerous effects, mainly oxidative stress and interference with functions of essential cations such as magnesium and zinc [2]. Moreover, as studies confirm, lead is a risk for hypertension, while cadmium exposure promotes atherosclerosis through particular oxidative mechanisms, also because it can indirectly deplete antioxidants, such as glutathione, increasing reactive oxygen species (ROSs) [3].

On the contrary, some metal ions, such as copper, iron, and zinc, are essential for life, but their excess can also cause diseases. As an example, several researchers suggest a correlation between metal dyshomeostasis and neurodegenerative disorders [4]. In particular, many studies suggest that metals are involved in β-amyloid precipitation, causing neuronal damage in Alzheimer's disease (AD) [5], and one of the hypotheses related to Parkinson's disease (PD) is linked with high Fe levels in the brain that probably contribute to the deposition of Lewy bodies containing α-synuclein [5]. Amyotrophic lateral sclerosis (ALS) and prion protein disease (PPD) seem to be pathologies in which the biometals can play a crucial role as well [6].

A potential way to treat metal poisoning and to reduce symptoms of diseases involving metal dyshomeostasis is chelation therapy. The term "chelation" is derived from the Greek word "chela",

meaning the claw of the lobster and other crustaceans): it is suggested for caliper-like groups that function together as two units connecting a central metallic atom, forming heterocyclic rings [7].

Chelators bind metal ions and enhance their excretion, in order to cause a progressive decrease in their body concentration. Therefore, chelation therapy requires compounds with specific pharmacodynamic and pharmacokinetic characteristics which depend on the physical and chemical properties of the metal and the chelating group itself such as ionic radius, solvation sphere size and deformability, hardness/softness of electron donors and acceptors, bioavailability, metabolism, organ, and intra/extracellular-specific compartmentalization [8]. Moreover, the thermodynamic, kinetic, and redox stability of the compounds is considered important. Although several chelators exhibit high thermodynamic stability and inertness, their redox potential falls itself into the range of ROS production [9]. An excellent chelator should have selectivity towards a specific target metal ion and should have low toxicity both as a free chelating agent and as a formed complex [10]. Another important requirement of chelating agents used for the treatment of neurodegenerative diseases is the ability to cross the blood–brain barrier (BBB). Consequently, a significant number of metal chelators are excluded because of their hydrophilicity [6]. Chelators can be classified on the basis of donor atoms involved, ring size (four-, five-, or six-membered), charge of the complex, or number of bonds between metal and chelating molecules (monodentate 1:1, bidentate 1:2, tridentate 1:3, tetradentate 1:4) [11].

The choice of a suitable chelating group for each metal ion is based on Pearson's theory of Hard and Soft Acid and Bases (HSAB; Table 1), that classifies Lewis acids and bases as hard, soft and borderline. "Hard" acids (named class (a) by Pearson) prefer to bind "hard" or nonpolarizable bases; on the contrary, "soft" acids, or class (b), bind preferentially "soft" or polarizable bases [12]. In chelation, metal ions are acids, while coordinating groups are bases: hard acids such as Fe^{3+}, Ca^{2+}, Al^{3+}, prefer to bind oxygen and nitrogen: soft acids such as Cu^{+}, Hg^{2+}, Ag^{+}, prefer sulfur; borderline acids such as Fe^{2+}, Zn^{2+}, Pb^{2+}, bind sulfur, oxygen, and nitrogen. Borderline ions show different preferences: for example, Pb^{2+} prefers oxygen and sulfur rather than nitrogen [13], while Cu^{2+} and Zn^{2+} prefer interacting with nitrogen over oxygen [14].

Table 1. Classification of Lewis acid and bases according to the Hard and Soft Acid and Bases (HSAB) theory.

	Acids	Bases
Hard	H^{+}, Li^{+}, Na^{+}, K^{+}, Be^{2+}, Mg^{2+}, Fe^{3+}, Ca^{2+}, Cr^{2+}, Cr^{3+}, Al^{3+}, SO_3, BF_3	F^{-}, OH^{-}, H_2O, NH_3, $CO_3{}^{2-}$, $NO_3{}^{-}$, O^{2-}, $SO_4{}^{2-}$, $PO_4{}^{3-}$, $ClO_4{}^{-}$
Borderline	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, SO_2, BBr_3	$NO_2{}^{-}$, $SO_3{}^{2-}$, Br^{-}, $N_3{}^{-}$, N_2, C_6H_5N, SCN^{-}
Soft	Cu^{+}, Au^{+}, Ag^{+}, Tl^{+}, $Hg_2{}^{2+}$, Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, BH_3	H^{-}, R^{-}, CN^{-}, CO, I^{-}, SCN^{-}, R_3P, C_6H_5, R_2S

Targeting Zn^{2+} is particularly important in medicinal chemistry, considering its role in the onset of neurodegenerative diseases and its occurrence with catalytic or structural functions in numerous enzymes involved in physiological and pathological pathways.

2. Zinc Binding Groups in Chelation Therapy

Zinc plays an essential role in living systems. It is one of the most abundant metals in the human body and it is common in the brain. Free zinc ions localize in glutamatergic nerve terminals where they are released upon terminal activation, besides they can act as antagonists of NMDA (N-methyl-D-aspartate) receptor [15]. Bound zinc has various roles, functioning as a cofactor in several proteins and enzymes. According to the classification as a "borderline" acid, Zn^{2+} coordinates nitrogen, oxygen or sulfur of amino acid residues in protein zinc binding sites: nitrogen of histidine is the most common one, followed by sulfur of cysteine, oxygen of aspartate/glutamate, but also carbonyl oxygen of peptide bond, carbonyl oxygen of asparagine/glutamine, and hydroxyl of tyrosine [16]. Zinc is also

required in functions such as cellular proliferation, differentiation and apoptosis, and immunity and reproduction [17]. Considering the importance of zinc, the perturbation of its homeostasis because of genetic alterations or diet deficiency causes a series of diseases [18].

Drugs containing a zinc binding group (ZBG) represent a way to treat disorders linked to zinc dyshomeostasis. This review focuses attention on recent ZBGs potentially useful for the treatment of Alzheimer's disease (AD), a neurodegenerative disorder, and for the inhibition of two zinc-enzymes, matrix metalloproteinases (MMPs) and carbonic anhydrases (CAs), involved in several pathologies.

2.1. Treatment of Alzheimer's Disease

Among other causes, the abnormal aggregation of the β-amyloid (Aβ) protein in the brain is involved in Alzheimer's disease (AD) [19,20]. It is demonstrated that Aβ chelates Cu^{2+}, Zn^{2+}, therefore these metals play an important role in protein precipitation and plaque formation as well as Fe^{3+} and Al^{3+} [21]. Some authors associated the formation of these aggregates to the production of reactive oxygen species (ROS) that lead to an increase in intracellular calcium levels, with consequent lipid peroxidation, mitochondrial dysfunctions, and neuronal inflammation [22]. The use of chelating agents capable of mainly crossing the blood–brain barrier (BBB) is a feasible strategy for the treatment of AD, since they could bind zinc, copper and iron ions (both free and accumulated within Aβ) without interfering with the activity of metalloenzymes [23].

Another important feature of chelators is the selectivity towards the different cations. Since only $Cu^{+/2+}$ directly catalyze the overproduction of ROSs (Zn^{2+} is a redox inert), it is, of course, the preferred target in chelation therapy. Moreover, Cu^{2+} and Zn^{2+} bind to the same amino acid residues of the Aβ peptide, so they are in competition in the inter-synaptic space for both proteins and chelators. Considering that Zn^{2+} is involved in neurotransmission and its significant removal can cause damages, Cu^{2+} can be identified again as the main target for potential anti-AD drugs. Starting from these considerations, it seems crucial that the chelator must have a higher Cu^{2+} over Zn^{2+} selectivity than those of Aβ peptide (calculated as ca. 4 orders of magnitude) [24,25].

The most commonly used moiety in the design of chelating agents for the treatment of AD is 8-hydroxyquinoline, a monobasic group that contains both nitrogen and oxygen atoms: it is a monobasic bidentate ligand and forms neutral 3:1 complexes with Fe^{3+} and 2:1 complexes with Zn^{2+} and Cu^{2+}, removing these metals from cells [26].

Clioquinol (CQ) is an 8-hydroxyquinoline analog that chelates Zn^{2+} and Cu^{2+} with higher affinity than Mg^{2+} and Ca^{2+} and with the suitable selectivity [27], which makes it capable of solubilizing Zn/Cu-assembled deposits in Aβ and inhibit Aβ redox chemistry. Moreover, CQ is hydrophobic and crosses the BBB easily, making it a candidate drug for oral treatment of Alzheimer's disease [28]. The structural characteristics of the Zn^{2+} and Cu^{2+} complexes of CQ have been known since 2004: after deprotonation of its phenolic oxygen, it forms neutral 2:1 complexes with both ions, where the pyridine nitrogen and the phenolate oxygen are metal donors of the bidentate ligand [29]. The structure of CQ is reported in Figure 1, as well as the supposed chelation mechanism. Unfortunately, studies show that CQ can be neurotoxic, probably because it removes metal ions not only from Aβ but also from other proteins, resulting in a mobilization of ions that causes oxidant effects if the CQ–metal complex is redox-active [30].

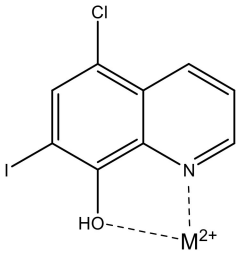

Figure 1. Clioquinol.

Metal chelators could be useful as a radiopharmaceutical for the determination of metal distribution and concentration in the brain by positron emission tomography (PET) or single-photon emission computed tomography (SPECT) [31]. A possible radiolabeled compound is ^{123}I-CQ, but unfortunately, it cannot be useful because of its radio-deiodination in vivo and low brain uptake. For this reason, CQ analogs were developed as potential drug candidates and PET ligands [31]. In particular, six analogs (Figure 2) with other halides (F, Cl, and Br) instead of the labile I in various positions were synthesized, with the aim of improving the stability of the molecules and modulate the acidity of phenolic OH: they have EC_{50} values comparable with CQ (2.3–5.2 μM), besides compounds **2d**–**2f** show an improved Cu and Zn ionophore capacity. The introduction of radiolabeled ^{18}F makes them potential PET biomarkers [31].

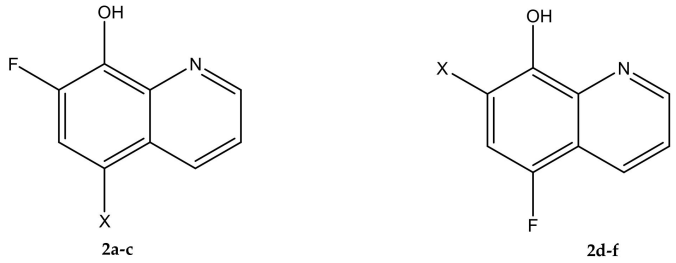

Figure 2. Analogs of clioquinol (CQ). X=Cl, Br, I [31].

The use of tetradentate ligands is another possible strategy to increase the protection against Aβ precipitation in AD. One such ligand, containing two 8-hydroxyquinoline (8-HQ) moieties covalently linked is shown in Figure 3. This molecule in particular can form coordinating complexes with Zn^{2+} and Cu^{2+}, in which both quinolines chelate metal ions. The linker is a methylene at the C2 position of each quinoline, so this compound is symmetric and without chiral centers. Both the ligand and its Cu^{2+} and Zn^{2+} complexes are small, neutral at physiological pH, and hydrophobic: these characteristics facilitate the crossing of the BBB, an already mentioned essential requirement for the compound's action against Aβ aggregation in Alzheimer's disease. Consequently, it can be considered a good starting point for the development of tetradentate ligands as therapeutic agents. [32].

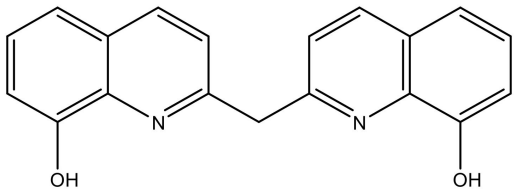

Figure 3. Tetradentate ligand designed by Dereave et al. [32].

Moreover, a series of quinoline-indole derivatives, based on the combination of an indole moiety with a CQ-derived one, was recently developed. This series produced compound WI-1758 (shown in Figure 4), endowed with excellent antioxidant activity, BBB penetration, and inhibition of Aβ self-induced aggregation. WI-1758 is also able to chelate Cu^{2+}, Zn^{2+}, Fe^{2+}, and Fe^{3+}. WI-1758 hydrochloride has a good pharmacokinetic profile with an oral bioavailability of 14.1% and the ability to permeate BBB in vivo (LogBB value of −0.19), besides its chronic oral administration ameliorated deficits in APP/PS1 AD mice and reduced Aβ deposits [33].

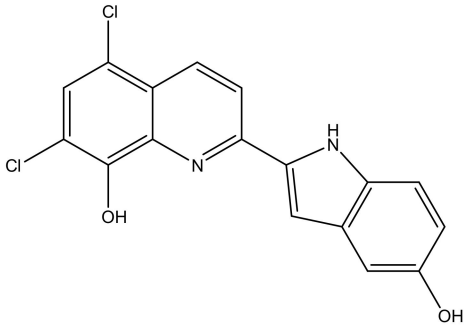

Figure 4. Compound WI-1758 [33].

Another recent approach aimed to combine the antioxidant and neuroprotective properties of (R)-alpha-lipoic acid (LA) and the chelating capacity of 8-HQ, resulting in a novel multitarget ligand (**5a**, in Figure 5), with antioxidant, chelating and neuroprotective properties for the treatment of neurodegenerative disorders, such as AD and PD [34]. The 8-HQ derivative 5-hydroxymethyl-8-hydroxyquinoline is linked to two molecules of LA via two ester bonds increasing its lipophilicity and it can cross plasma membranes, releasing HQ and two molecules of LA. This compound seems to be better than the single LA and HQ for neuroprotective and antioxidant activities [34]. Another 8-HQ analog, with the hydroxymethyl moiety linked to the sulfhydryl group of a glutathione tripeptide (GSH), was recently developed and displayed antioxidant activity (**5b**, Figure 5). The increased lipophilicity of the molecule is caused by the conjugation of the GSH's free cysteine to the HQ group. In addition to the antioxidant activity, the coordination properties of this GS(HQ)H toward Zn^{2+}, and Cu^{2+} were also studied. The K_D values calculated for the Cu^{2+} and Zn^{2+} ligand investigated systems were 280 pm and 0.57 mm, respectively. These values suggest that GS(HQ)H is only partially able to remove copper from the Aβ once formed [35].

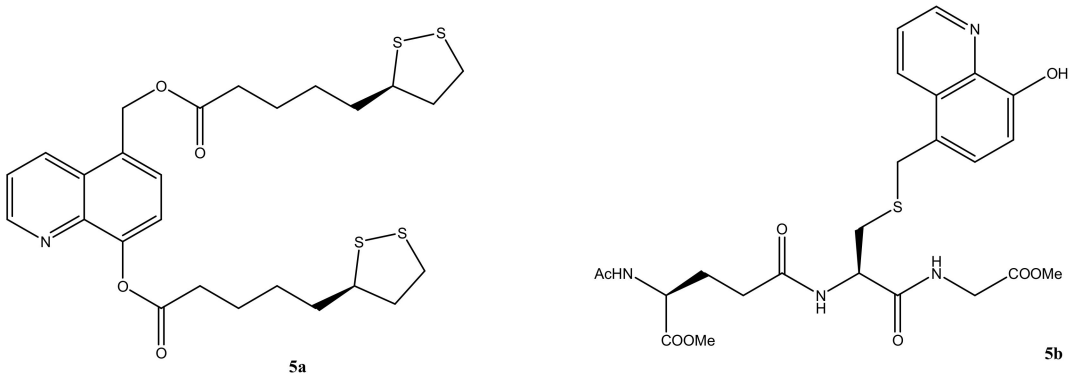

Figure 5. Structures of 8-hydroxyquinoline (8-HQ) analogs [34,35].

In order to tackle the multifactorial etiopathogenesis of AD, several efforts have been made in recent years to find multitarget anti-AD drugs. One notable approach consisted in combining Acetylcholinesterase (AChE) inhibition with other neuroprotective functions such as metal chelation. This was achieved via the development of hybrid molecules, combining a tacrine (TAC) unit or a moiety mimicking of donepezil (DPZ) benzylpiperidine with Zn^{2+} and Cu^{2+} chelating moieties. In particular, 2-hydroxyphenol-benzimidazole moiety (BIM) has been chosen because it can bind ions as a bidentate chelator thanks to its N and O donor atoms (Figure 6). Several BIM-hybrids (**6a–c**, namely PP-BIM, PZ-BIM, and TAC-BIM1 are reported as an example in Figure 6) showed a good chelating action towards Cu^{2+} (pM = 10.7–11.1) and a moderate one towards Zn^{2+} (pM = 6.3–6.4), forming 1:1 and 1:2 complexes. Importantly, the moderate Zn^{2+} chelation does not lead to its depletion in synaptic keys, according to the requested selectivity profile [25]. Meanwhile, **6a–6c** and derivatives showed

numerous additional properties that candidate them for future development on the road of multitarget therapy for AD [36–39].

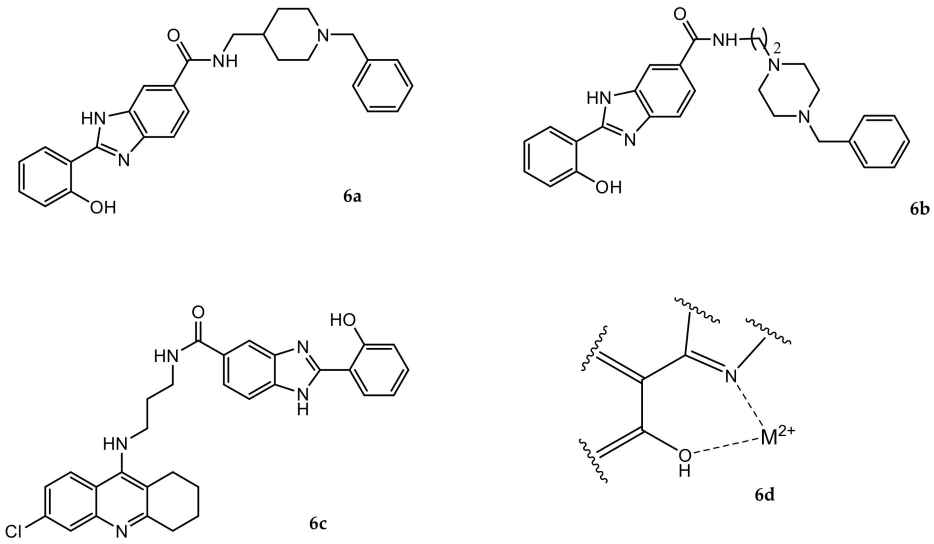

Figure 6. Structures of PP-BIM (**6a**); PZ-BIM (**6b**); and TAC-BIM (**6c**); and their supposed chelation mechanism (**6d**) [25].

Among bifunctional molecules (metal chelation, Figure 7, and Aβ interactions), compound **7a** (Figure 7) reduced metal-Aβ neurotoxicity via the modulation of ROS production and of metal-induced Aβ aggregation. However, its limited solubility in water impedes its application. Similar compounds **7b** and **7c** (Figure 7), are able to interact with both Aβ species and metal ions, as demonstrated by spectroscopic methods such as high-resolution NMR spectroscopy and UV–vis spectroscopy and are more stable than **7a**. Meanwhile, **7b** and **7c** can chelate Zn^{2+} and Cu^{2+} through two N donor atoms. In particular, **7c** is in contact with both Zn^{2+} and Aβ, forming a **7c** -Zn^{2+}-Aβ complex that leads to the control of metal-induced Aβ aggregation [40].

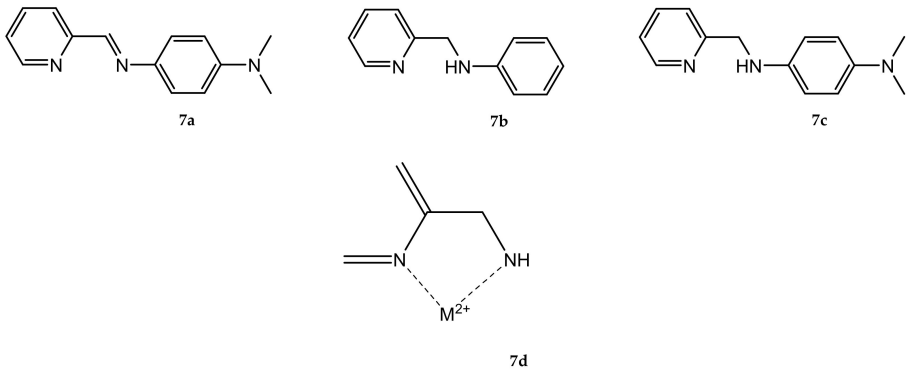

Figure 7. Bifunctional molecules for the treatment of Alzheimer's disease (AD) and their supposed chelation mechanism (**7d**) [40].

2.2. *Inhibition of Matrix Metalloproteinases*

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases. They are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan [41]. Their overexpression is associated with many diseases, such as cancer and chronic inflammation. MMP inhibitors (MMPIs) usually contain a zinc binding group (ZBG) linked to a backbone that interacts with the specificity pocket S1′ [42]. For this reason, the essential requirement for a MMPI is the presence of a group that may be able to

bind or better chelate Zn^{2+} in the active site of the enzyme [43]. The majority of MMPIs belong to the classes of carboxylic acids, hydroxamic acids, thiols, phosphorus-based ligands or sulfodiimines, and others [42,44].

Among MMPs, the gelatinase subfamily, consisting of gelatinase A (MMP-2) and gelatinase B (MMP-9), is involved in pathological events leading to cancer, inflammatory diseases, cardiovascular diseases, and neurological disorders [45]. Recently α-sulfonamide-based hydroxamates proved to be interesting MMP inhibitors, due to the hydroxamate moiety's activity as a ZBG, while the sulfonyl group forms an important hydrogen bond with the enzyme's peptidic backbone. In this regard, a new series of compounds (Figure 8) endowed with good potency and selectivity for MMP-2 and MMP-9, without inhibition of MMP-1 was recently described: the sulfonyl group was moved from α- to β-position, while in α-position a linker consisting of a heteroatom such as O or N replaced the sulfonamide, with the possibility to chelate zinc with an improved MMP-9 inhibition at the nanomolar range, although the authors report the classical bidentate mechanism of hydroxamic acids as being the most likely [45].

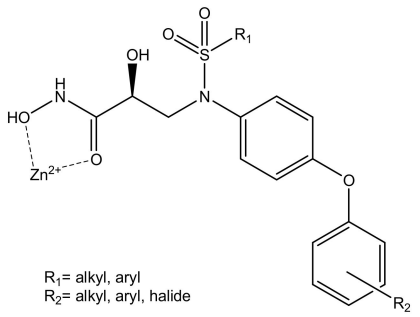

Figure 8. General structure of zinc chelators [44].

A subsequent work of the same group studied the introduction and the optimization of an α-amino substituent in a series of congeners. This modification leads to new MMP-2/MMP-9 inhibitors characterized by improved inhibitory activities and ADME properties. In particular, compounds containing the α-cyclic amino group showed low protein binding, good water solubility, and enhanced pharmacokinetic properties [46].

Nuti et al. reported the synthesis and in vitro evaluation of a new series of selective MMP-13 inhibitors. MMP-13 catalyzes the hydrolysis of type II collagen (the main structural component of the cartilage matrix) and high levels of MMP-13 are associated with diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) and is an important therapeutic target [47]. The reported compounds are N-isopropyloxy-arylsulfonamides in which different aryl substituents on the sulfonamidic portion are introduced. Among these inhibitors, the compound shown in Figure 9 exhibited a nanomolar inhibiting activity for MMP-13 (IC_{50} = 3.0 ± 0.2 nM) and was highly selective for this enzyme compared to other MMPs. They tried to explain this selectivity through the investigation of binding between the compound and MMP-13 in a docking study, but they concluded that X-ray crystallography is necessary to elucidate the mechanism of coordination and inhibition [48].

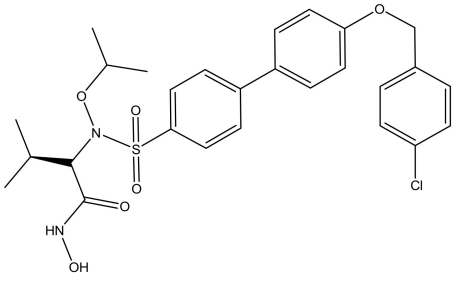

Figure 9. MMP-13 inhibitor synthesized by Nuti et al. [48].

Unfortunately, hydroxamic acids are frequently affected by rapid excretion, low oral bioavailability, and in vivo hydrolysis since their discovery in 90 s [49], which encouraged the development of alternative ZBGs.

As an example, following this strategy, a novel class of compounds (Figure 10), consisting of pyrimidine compounds which possess a 1,2,4-triazol-3-yl group as a zinc binding group (ZBG) were recently developed and proved useful in the inhibition of MMP-13 up to the low nanomolar range, with high selectivity against MMP-2, -9 and -10. X-ray analysis of the complex shows that 1,2,4-triaziol-yl moiety directly binds zinc, without chelation (with a ligand to metal molar ratio 4:1), differently from what can be supposed looking at the chemical structure [50].

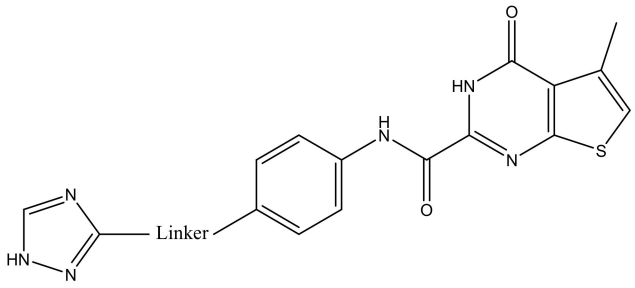

Figure 10. General structure of pyrimidine-based compounds as MMP-13 inhibitors [50].

On the other hand, Puerta and collaborators already identified in 2003 six new potential ZBGs (Figure 11) that will be useful for the subsequent development of MMP inhibitors able to bind Zn^{2+} in MMPs pocket in a strong, bidentate way [51]. They found an alternative to hydroxamate through the study of the interaction of six different scaffolds with the tetrahedral zinc complex [($Tp^{Ph,Me}$)ZnOH], ($Tp^{Ph,Me}$ = hydrotris(3,5-phenylmethylpyrazolyl)borate, Figure 10). Thanks to X-ray crystallography and IR and ^{1}H-NMR data, it was demonstrated that these ZBGs are able to interact with the metal through chelation [51].

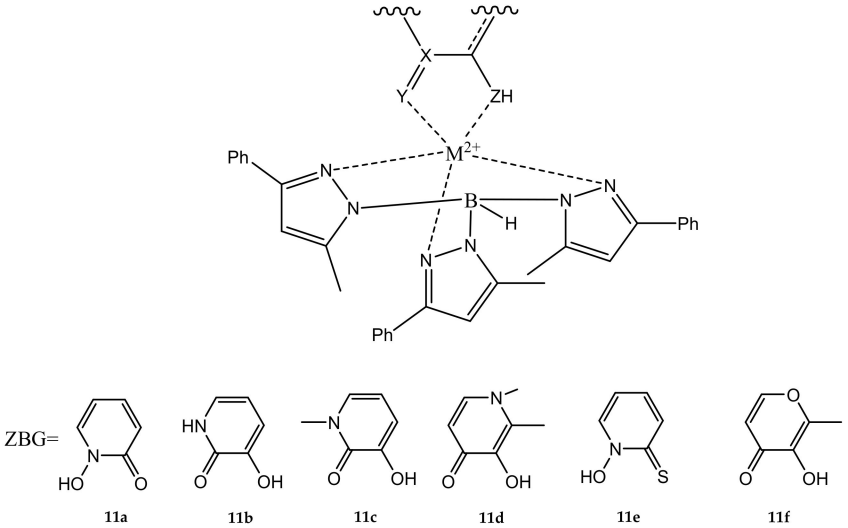

Figure 11. Zinc binding groups (ZBGs) in [($Tp^{Ph,Me}$)Zn(ZBG)] complexes: 1-hydroxy-2(1H)-pyridinone (**11a**); 3-hydroxy-2(1H)-pyridinone (**11b**); 3-hydroxy-1-methyl-2(1H)-pyridinone (**11c**); 3-hydroxy-1,2-dimethyl-4(1H)-pyridinone (**11d**); 1-hydroxy-2(1H)-pyridinethione (**11e**); 3-hydroxy- 2-methyl-4-pyrone (**11f**) [51].

Further development of this route led to a new class of compounds with a 1-hydroxypiperazine-2,6-dione (HPD) as the ZBG of choice for the inhibition of matrix metalloproteinases (Figure 12). HBD binds the catalytic Zn^{2+} of MMPs in a bidentate way, such as the hydroxamic acids, but its

six-membered ring structure should give it greater stability and more resistance to hydrolysis, with, additionally, better pharmacokinetic properties [52]. The inhibition against a wide panel of MMPs was reported with IC_{50} from the nanomolar to low micromolar range [52].

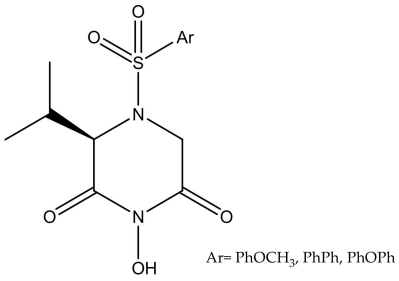

Figure 12. 1-hydroxypiperazine-2,6-dione (HPD) derivatives [52].

Zhang et al. synthesized instead the first series of 1-hydroxy-2-pyridinone-based sulfonamide inhibitors of both MMP-2 and MMP-9. These compounds show nanomolar potency in the enzyme assay. Moreover, one of the derivatives (Figure 13) demonstrates excellent pharmacokinetic properties in rats, with oral bioavailability and reduced brain edema caused by ischemia in mice [53].

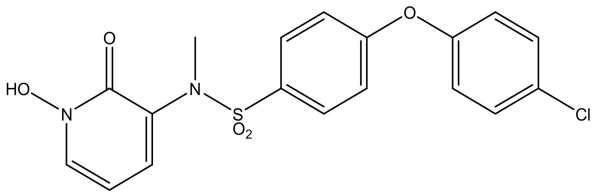

Figure 13. Best inhibitor synthesized by Zhang et al. [53].

Another example of an alternative to the hydroxamic acid as the ZBG, namely a hydroxypyrone moiety (with a supposed mechanism already reported in Figure 10), was developed by Aerts and collaborators [54]. In their series a terphenyl group interacts with the aminoacidic residues in the S^1 pocket of the MMP catalytic domain. In particular, the compound shown in Figure 14 exhibits an interesting potency and selectivity towards MMP-12 with an IC_{50} in the nanomolar range (0.117 nM) with good-high selectivity against the other MMPs (it is more than 250 times more active then on MMP-1,-3,-7,-9,-10, and -13). Interestingly, it possesses also anti-inflammatory properties in vitro and in vivo [54].

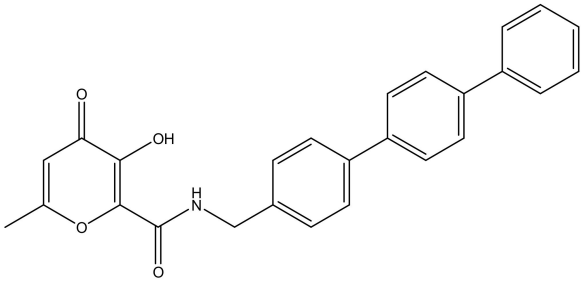

Figure 14. Best hydroxypyrone-based matrix metalloproteinases inhibitor (MMPI) developed by Aerts et al. [54].

Other innovative noncyclic but rigid scaffolds have been studied as inhibitors of MMP-2, MMP-3, and MMP-8: this particular moiety contains the CO–NH–OH groups necessary for zinc chelation. An Italian group [55], for example, demonstrated that the binding interactions of the hydroxamate (Figure 15, compound **15a**) can be maintained in a series of N-hydroxyurea derivatives (Figure 15, compound **15b–e**). In the first instance, the crystal structure of the complex with MMP-8 showed

that the N-hydroxyurea, in contrast with the analogous hydroxamate, coordinates the catalytic zinc ion in a monodentate fashion, rather than a bidentate one, and with high out-of-plane distortion of the amide bonds. Therefore, N-hydroxyureas showed a decrease in binding affinity compared to hydroxamate analogs. This profile was explained through conformational differences: N-hydroxyureas prefer the trans-conformation of the N_1-CO amide bond, which is unfavorable for zinc chelation, while hydroxamate moiety generally adopts a more favorable cis-conformation of the N_1-CO amide bond. This led researchers to introduce some modifications, such as N_3-metylation, in order to prevent the trans-conformation and obtain, finally, zinc chelation [55].

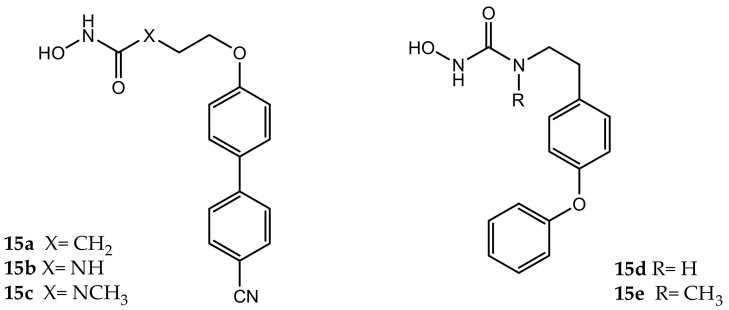

Figure 15. Compounds **15a–e** [55].

Finally, Rubino et al. evaluated the inhibition activity of 40 phenolic fragment compounds against MMP-2, -8, -9, and -14, which could be new ZBG with enhanced selectivity and affinity for Zn^{2+}. Phenols containing hydroxy and amino moieties in ortho- or para-position are effective MMP inhibitors, such as catechol (Figure 16) which showed a very interesting activity on all tested MMPs with a good selectivity towards MMP-2 [56]. Unfortunately, subsequent studies of the same group demonstrate the instability of catechol as well as a probable monodentate interaction of this moiety with Zn^{2+} in MMPs pocket [57].

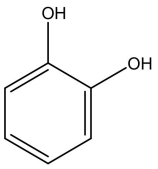

Figure 16. Catechol.

2.3. Inhibition of Carbonic Anhydrases

Carbonic anhydrases (CAs) are zinc metalloenzymes that catalyze the physiological reaction of carbon dioxide hydration to bicarbonate and protons. Five distinct enzyme families of CAs are known: α, β, γ, δ, and ζ. Inhibitors of human α-CAs (CAi) can be used for several clinical applications, such as antiglaucoma, anticonvulsant, diuretics, and recently as anticancer agents [58]. CAi can be divided into two main classes: those that bind the catalytic zinc ion in the enzyme active site, and those that are bound to the active site but do not interact directly with the metal ion. Among CAi containing a ZBG, four different groups have been studied with crystallography: the ureates/hydroxamates, the mercaptophenols, the metal-complexing anions, and the sulfonamides with their bioisosteres, such as sulfamates and sulfamides [59].

Primary sulfonamides are the most important class of human CA I and II inhibitors. The pharmacophoric sulfonamide group coordinates Zn^{2+} in the enzyme's active site, while the substituents in the benzene ring linked to the sulfonamide group are responsible for the further interactions. Krasavin et al. designed diaryl sulfonamides containing a 1,3-oxazole moiety (Figure 17, compounds **17a–d**) which can interact with both the lipophilic and hydrophilic sides of the enzyme's

active site. Some of these compounds showed inhibitory activity in the picomolar range towards CA I and CA II [60].

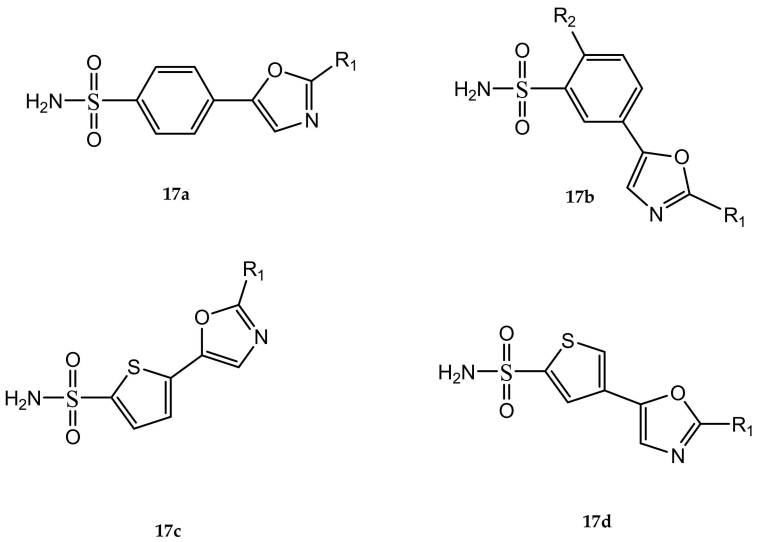

Figure 17. General structures of 5-(sulfamoyl)-aryl-1,3-oxazoles designed by Krasavin et al. [60] R_1 = alk, R_2 = alk.

It was more recently demonstrated that the introduction of hydroxy and methoxy moieties at the sulfonamide nitrogen can lead to the development of more selective CAIs. Moreover, the effect of the substitution in benzene-sulfonamide (Figure 18, compounds **18a–c**) of sulfonamide moiety with a hydroxamate group (Figure 18, compound **18d**) was also explored, reporting the inhibitory activity of all catalytically active hCA isoforms and two MMPs (MMP-2 and MMP-8). In particular, cytosolic isoforms hCA I and hCA II are weakly inhibited by the hydroxamate 19-d and highly or moderately inhibited by the sulfonamides **18a–c**; meanwhile, **18d** shows a potent inhibition (inhibition constant in the range of 0.94–9.51 µM) of transmembrane isoforms hCA XII and hCA XIV, important potential drug targets for glaucoma and cancer. Lastly, X-ray crystallography of the hydroxamate N-hydroxy-benzamide (**18d**) showed that it binds to the hCA II active site with the CO and OH groups which both coordinate to the zinc ion, forming an energetically favored five-membered chelate complex [61].

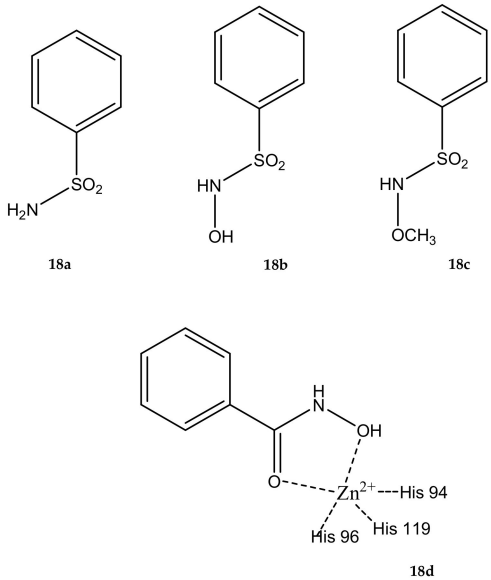

Figure 18. Compounds **18a–d** [61].

Some groups can be useful as ZBGs of both MMPs and CAs. Puerta et al. developed a series of heterocyclic ZBGs as an alternative to the most commonly used hydroxamic acid for the inhibition of MMPs [62]. In particular, four groups were studied as zinc-chelating portions: hydroxypyridinones, pyrones, hydroxypyridinethiones, and thiopyrones. These compounds were evaluated against MMP-1, -2, and -3 in different conditions, and the results suggest that they could be potent, nontoxic, and biocompatible alternatives to the hydroxamic acid chelator available for use in MMPIs. The cyclic structures in MMPIs reveal enhanced bioavailability and biostability [62]. Four of these compounds (reported in Figure 19) were also studied as inhibitors of CAs. The crystal structure of CA II in complex with 1,2-HOPTO (Figure 19, compound **19d**) was determined and revealed an interesting bidentate chelating mode with Zn^{2+}, similar to those reported for compound **18d** (Figure 18, involving His94, His96 and His119). Moreover, 1,2-HOPTO interacts with the Thr199 and Thr200 residues of the active site and it is involved in a hydrogen-bonding network that is translated via water molecules within the entire active site of CA II. [63]. This study led the way to a series of derivatives synthesized over the years bearing these scaffolds as essential for the activity on both enzymes [20,62–64].

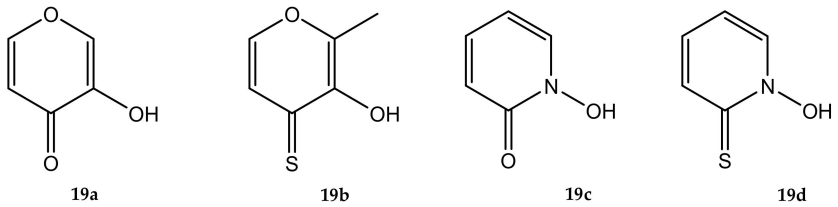

Figure 19. ZBGs of both MMPs and carbonic anhydrases (CAs) [61,62].

3. Conclusions

Metal chelation is a necessary weapon for medicinal chemists. In particular, zinc (II) is an important target for the therapy of cancer (targeting metalloenzymes such as MMPs and CAs) and Alzheimer's disease (in multitarget approaches, joined with Cu^{2+} chelation). Natural [1,20,65] and synthetic [1,20,22,42,64] compounds have been tested over the years with different approaches and valuable results have been reached regarding the ability of these substances in sequestering several cations. The challenge will be now specific targeting and better selectivity, in order to avoid the side effects due to the significance of Zn^{2+} also in numerous physiological pathways in specific districts of the human organism.

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