

Article

Molecular Docking Study of Praeruptorin A-H and Qianhu coumarin A-J Binding to Divalent Metal Transporter-1 (DMT1)

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Abstract

The divalent metal transporter DMT1 (SLC11A2) is implicated in diverse human pathologies including cancers, inflammatory and degenerative diseases. Small molecules targeting this membrane protein are actively searched. Following the identification of the pyranocoumarin praeruptorin A as an inhibitor of ferroptosis that is able to bind to DMT1, we have investigated the interaction of related natural products with DMT1 using molecular modeling to determine structure-binding relationships. Two series of compounds were tested: praeruptorins A-H and qianhu coumarins A-J, all isolated previously from the roots of the Chinese medicinal plant *Peucedanum praeruptorum* Dunn (Bai-Hua Qian-Hu). The antitumor compound praeruptorin C was identified as the best DMT1 ligand in the series, with a binding capacity largely superior to that of praeruptorin A and also well superior to the reference organoselenium product ebselen, at least from an in silico perspective. Praeruptorin C, and to a lower extent praeruptorins F and H, can form stable complexes with DMT1 upon binding close to the ebselen binding site. Qianhu coumarins C and I were also identified as potential binders. Altogether, the analysis of the 18 natural products enabled identification of structural elements implicated in the target binding process. The curvature of the tricyclic pyranocoumarin scaffold and the angeloyl side chain at position 9 seem to contribute importantly to the protein interaction. An experimental validation is required but the docking study paves the way to the discovery and design of tricyclic coumarin derivatives targeting DMT1.

Keywords: DMT1; metal transporter; molecular docking; praeruptorin; qianhu coumarin; SLC11A2



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1. Introduction

The protein Divalent Metal Transporter 1 (hereafter DMT1), also known as NRAMP2 (natural resistance-associated macrophage protein 2) or SLC11A2 (solute carrier family 11 member 2), plays major roles in the transportation of metal ions, notably Fe²⁺, Mn²⁺, Co²⁺, and Cd²⁺. It is a broad specificity metal cation transporter with, in particular, a key role in the transport of ferrous iron in the intestinal epithelium. This secondary metal transporter is expressed at the membrane of various cells, notably the apical membrane of enterocytes

of the duodenal brush border. It is also expressed on renal tubules to regulate the transport of divalent cations in coordination with other protein partners (Figure 1). Through the sequestration of metals, this protein contributes to the defense of the epithelium against enteric bacteria [1].

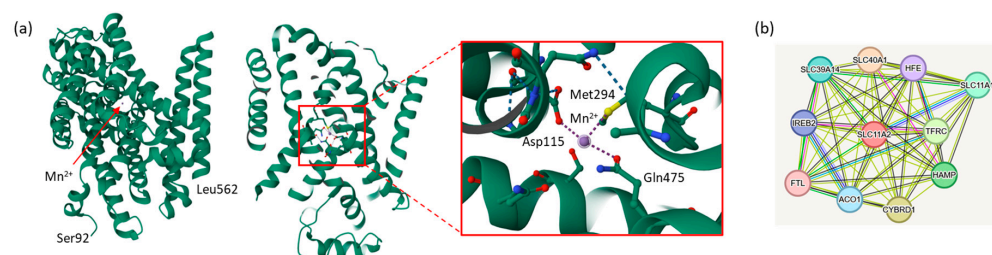


Figure 1. (a) A model of DMT1 in complex with Mn^{2+} with a detailed view of the metal complex (from PDB: 9F6N). (b) The protein partners of DMT1 include the transferrin receptor protein 1 (TFR1), iron-responsive element-binding protein 2 (IREB2), cytochrome b reductase 1 (CYBRD1), and a few other proteins. Interactome created with String v.12.0 (String Consortium 2023, accessed on 17 April 2026, <https://string-db.org/>).

There are two related proteins, SLC11A1 and SLC11A2, with pivotal roles in iron metabolism and cellular homeostasis. These processes are intricately linked to oncogenesis. SLC11A1 is expressed primarily in macrophages, acting as a modulator of the immune response and the regulation of the tumor microenvironment. SLC11A2 is ubiquitously expressed and plays a major role in the regulation of iron-dependent programmed cell death (ferroptosis). In recent years, SLC11A2/DMT1 has emerged as a therapeutic target in oncology, notably to control cell proliferation, metastatic progression and immune response [2]. A recent study pointed out the overexpression of DMT1 mRNA in ovarian cancers and showed that the knockdown of DMT1 reduced ovarian cancer migration and the extent of apoptosis induced by the chemotherapeutic drug cisplatin [3]. For these reasons, inhibitors of DMT1 are actively searched. DMT1 inhibitors could be useful to improve cancer treatment but also to combat other pathologies associated with an elevated expression and/or a dysfunction of DMT1, notably inflammatory and degenerative diseases [4,5].

Modulators of DMT1 have been identified, notably benzylisothioureas, pyrazolyl-pyrimidone, pyrazolyl-pyridine derivatives and a few other synthetic molecules [6–11]. Specific screening assays have been set up to identify new DMT1 inhibitors [12] and fragment-based drug discovery approaches have been implemented to help the design of novel archetypes [13]. A few modest inhibitors of DMT1 have been identified from the GDB-17 library of fragments [14]. The triphenyl derivative LM22B-10 has been used as a SLC11A1 antagonist but it is also a ERK activator [15]. Ebselen is also a relatively potent and selective pharmacological inhibitor of DMT1 iron transport [16,17]. New inhibitors are needed to design drug candidates.

Drugs able to promote ferroptosis are considered of interest to kill iron-addicted cancer cells and in particular cancer stem cells which are often chemo-resistant and difficult to reach. Different ferroptosis-inducers have been identified, such as the alkaloid piper-longumine, and the polyether antibiotic salinomycin [18,19]. In head and neck cancer cells, salinomycin induced the same effects as those observed with shRNA-mediated DMT1 silencing but this natural product does not directly target DMT1 [20]. It sequesters iron in lysosomes, binds to nucleolin and other proteins in the stem cell niche [21–23]. On the opposite, the natural product praeruptorin A has been recently identified as an inhibitor of ferroptosis able to bind well to DMT1. This pyranocoumarin derivative was found to reduce oxidative damages caused by the anticancer drug doxorubicin in cardiac cells. The authors pointed out the formation of stable DMT1-praeruptorin A complexes [24].

Praeruptorin A is a well-studied inhibitor of ferroptosis, considered for the treatment of inflammatory pathologies, such as colitis, sepsis and chronic respiratory diseases [25–27]. The product has been isolated for the first time, in the early 1980s, from the roots of the Apiaceae plant *Peucedanum praeruptorum* Dunn. (Baihuaqianhu in Chinese) used in traditional medicine [28]. It was isolated together with its analog praeruptorin B (also known as anomalin) [29]. Over the years, eight praeruptorins A-to-H have been identified from plants [30] (Figure 2). In the present study, we have compared the capacity of all praeruptorins to form complexes with DMT1 and identified that praeruptorin C as the best binder in the series, largely superior to praeruptorin A and even better than the reference ebselen. This finding prompted us to search for related natural products as DMT1 binders. A series of ten little-known coumarin derivatives designated qianhuocoumarins A-J (Figure 3), also isolated from *Peucedanum praeruptorum* Dunn, were tested and two products were found to bind well to DMT1. The present docking analysis opens the door to the discovery of new DMT1 inhibitors of natural origin.

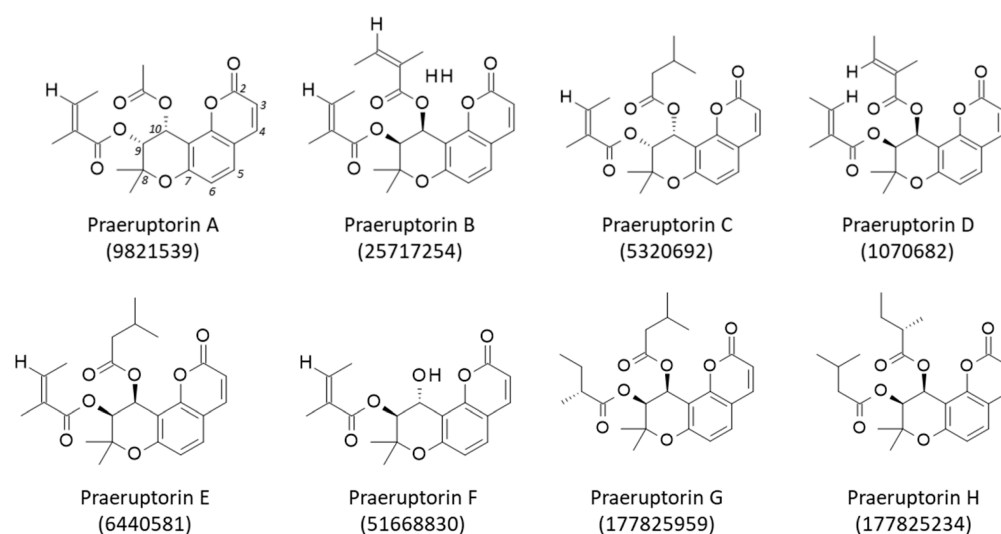


Figure 2. Chemical structures of praeruptorin A-H. For each molecule, the indicated number refers to the compound identity (CID) available on PubChem (<https://pubchem.ncbi.nlm.nih.gov/>).

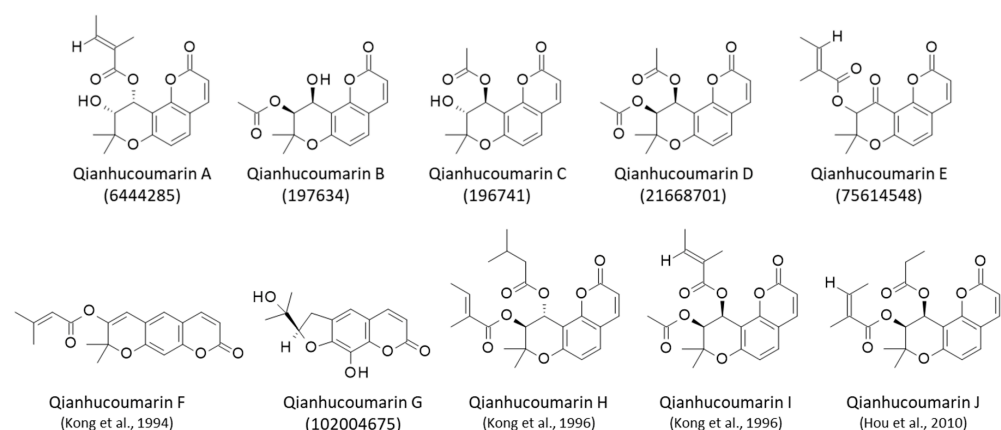


Figure 3. Chemical structures of qianhuocoumarins A-J. CID numbers are indicated, as in Figure 2 [31–34].

2. Materials and Methods

2.1. Natural Products, Molecular Structures and Software

The docking analysis was carried out using 18 test ligands (praeruptorin A-H and qianhuocoumarin A-J) and the control drug ebselen known to bind to DMT1. In most cases, the drug structure was retrieved from the PubChem data bank. For compounds not present in PubChem, their chemical structures were identified from the original publications. It was the case for qianhuocoumarin F [31], qianhuocoumarin H-I [32,33], and qianhuocoumarin J [34]. All compound structures were graphically represented and analyzed with the visualization tool from Biovia 2020 discovery studio (Dassault Systèmes, San Diego, CA, USA).

The molecular docking analysis was based on the electron microscopy structure (3.60 Å resolution) of the transmembrane human protein divalent metal transporter 1 (DMT1) complexed with Mn^{2+} [35,36]. The Mn^{2+} complexation was maintained during the Monte Carlo procedure. The single chain protein includes 471 amino acids (Ser92 to Leu562) and the drug binding site has been located in a central pocket, as represented in (Figure 1). The structure of the protein in a closed conformation (occluded state) was retrieved from the Protein Data Bank (code 9F6N). The combination of BOSS (v4.9) and GOLD (v5.3) softwares was used for the docking analysis. For each ligand, the conformers of minimum-energy were identified, compared and a single conformer was then selected. A conformational search procedure was applied using BOSS using a Monte Carlo (MC) simulation in the NPT ensemble at constant pressure, constant-temperature [37,38].

An analysis of the potential drug binding sites on DMT1 was performed using the freely accessible web server CASTpFold (Computed Atlas of Surface Topography of proteins) [39] (Figure 4). The drug binding site has been located at the apical pole of the DMT1 protein [24] which is represented here in an occluded state [40]. The same binding site has been considered in a study of the iridoid glycoside gentiopicoside binding to DMT1 [41]. The final molecular structures were analyzed using the molecular modeling program UCSF Chimera v1.15 (<http://www.cgl.ucsf.edu/chimera/> (accessed on 19 April 2026)).

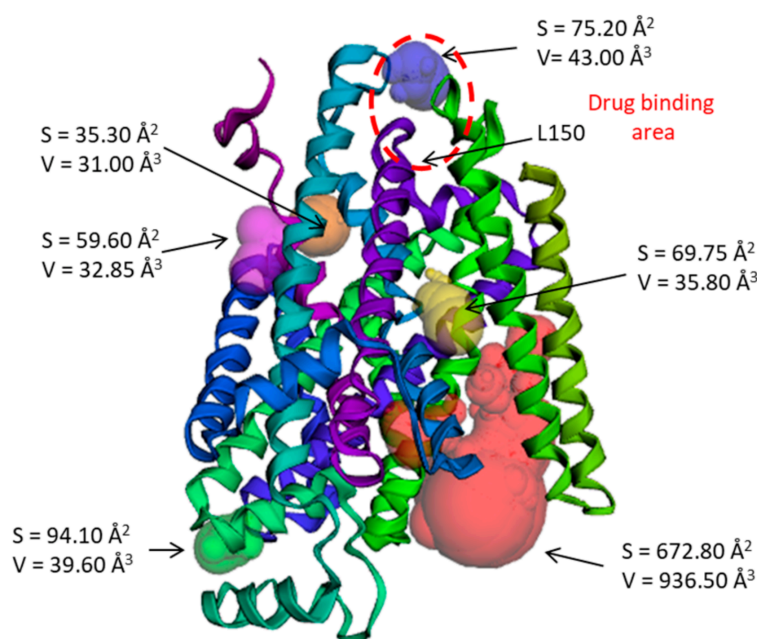


Figure 4. Binding site analysis of DMT1 (pdb: 9F6N) using web server CASTpFold (<https://cfold.bme.uic.edu/castpfold/>, accessed 19 April 2026). The drug binding zone corresponds to the area delimited in blue (surface of 75.2 Å² and a volume of 43.0 Å³) nearby the central Leu150 residue.

2.2. Molecular Docking Analysis

To drug binding site was located around residue Leu150 of DMT1 and this residue was set up as the center of the docking grid (Figure 5a). The side chains of amino acids Arg149, Leu150, Arg153, Leu154, Val157, Asn322, Phe326, Met496, Phe499, and Trp505 were rendered fully flexible during the docking process. A 10 Å sphere radius centered on the C α of Leu150 has been considered.

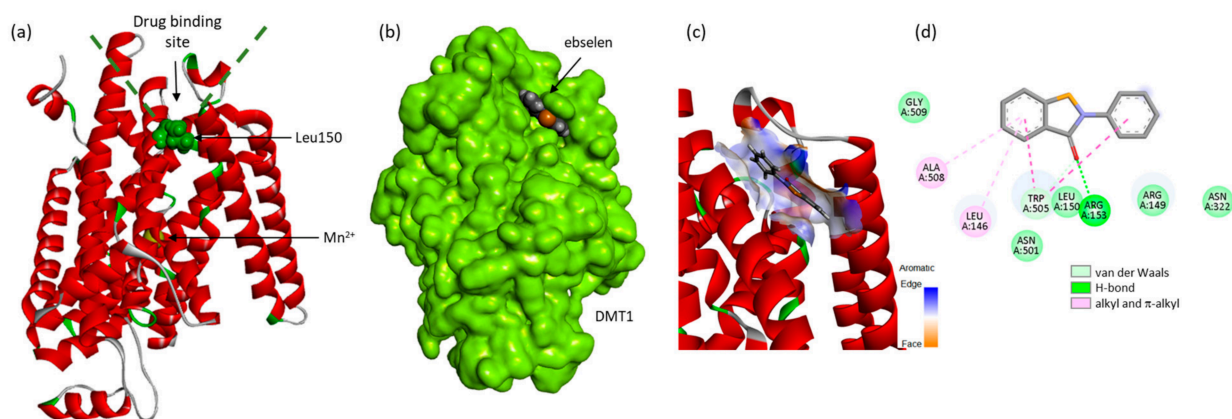


Figure 5. (a) Positioning of the drug binding site on DMT1, centered on residue Leu150. (b) Molecular model of ebselen bound to DMT1 (PDB: 9F6N). (c) A close-up view of the ebselen binding site. (d) Binding map contacts for ebselen bound to DMT1 (color code indicated).

The drug ebselen, known to bind to DMT1 [17], was used as a reference ligand and its binding to the defined site was validated (Figure 5). The best binding mode for each natural product in the praeruptorin and qianhucoumarin series was determined after selection of >100 poses, all valid from the energy analysis. The six best binding poses were ranked using the fitness scoring function with the help of the Piecewise Linear Potential (PLP) fitness function used to calculate the binding energies. The scoring function is incorporated into GOLD [42] which is considered a robust docking algorithm [43]. Tautomeric and protonation states are treated in GOLD using SMARTS patterns.

The extent of binding of the ligands to the protein target was determined through calculation of ΔE values which correspond to the empirical potential energy of the interaction. ΔE is calculated via the following equation: $\Delta E(\text{interaction}) = E(\text{complex}) - [E(\text{protein}) + E(\text{ligand})]$. For this purpose, the SPASIBA spectroscopic method was applied, with binding energies calculated using empirical molecular mechanics (MM) force field parameters [44,45]. The SPASIBA empirical force field parameters are integrated into CHARMM force field [46]. They take into account the crystal-phase infrared data and represent the vibrational frequencies with a better accuracy than molecular mechanics potentials. SPASIBA parameters have been obtained from both theoretical predictions and observed IR and Raman data for many types of molecules, including organic compounds, amino acids, and lipids [47].

The ΔG values, corresponding to the free energies of hydration, were determined via a MM/GBSA free energy analysis. The Molecular Mechanics/Generalized Born Surface Area procedure provides the same level of convergence as Molecular Dynamics (MD) but requires less computer time [38]. Gibb's free energy of binding (ΔG) takes into account the influence of H₂O molecules in the drug binding site [48]. Calculation of ΔG values was performed with the BOSS program which performs a Monte Carlo (MC) statistical mechanics simulation, and a standard energy minimization, normal mode analysis, and conformational searching. The docking procedure calculates the binding free energy, taking into account the hydration free energy of the ligand–receptor complex in

addition to those of the individual ligand and receptor [49]. This methodology has been used to study the interaction of different natural products with protein receptors [50–52].

3. Results

3.1. Binding of Praeruptorins to DMT1

The eight praeruptorin natural products were individually docked onto the DMT1 structure at the ebselen binding site. In each case, the best binding configuration was determined and the empirical energy of interaction (ΔE) and free energy of hydration (ΔG) were calculated (Table 1). The ΔE values reflect the stability of the drug–protein complex. Significant variations were observed within the series, with praeruptorin C emerging as the best in silico ligand, largely better than the reference product ebselen. The compounds rank in the order praeruptorin C > H > F > D > E > B > A > G for their capacity to form complexes with DMT1.

Table 1. Calculated potential energy of interaction (ΔE) and free energy of hydration (ΔG) values for the binding of praeruptorins and qianhuocoumarins to DMT1.

Compounds (CID) ¹	ΔE (kcal/mol)	ΔG (kcal/mol)
Ebselen (3194)	−73.65	−25.95
Praeruptorin A (9821539)	−59.05	−29.55
Praeruptorin B (25717254)	−61.50	−23.25
Praeruptorin C (5320692)	−81.80	−29.20
Praeruptorin D (1070682)	−71.20	−32.75
Praeruptorin E (6440581)	−69.05	−22.70
Praeruptorin F (51668830)	−73.90	−34.90
Praeruptorin G (177825959)	−54.85	−30.40
Praeruptorin H (177825234)	−76.75	−37.50
Qianhuocoumarin A (6444285)	−70.10	−36.50
Qianhuocoumarin B (197634)	−55.80	−32.90
Qianhuocoumarin C (196741)	−71.00	−29.30
Qianhuocoumarin D (21668701)	−58.70	−37.55
Qianhuocoumarin E (102004715) [9S] ²	−58.20	−35.65
Qianhuocoumarin F	−52.50	−30.40
Qianhuocoumarin G (102004675)	−50.40	−30.70
Qianhuocoumarin H	−60.60	−32.85
Qianhuocoumarin I	−71.50	−39.80
Qianhuocoumarin J (177824798)	−58.95	−35.50

¹ CID, compound identity numbers from the PubChem data bank. ² Qianhuocoumarin E (131676021) [9R]: ΔE = −51.10 kcal/mol; ΔG = 31.90 kcal/mol.

Praeruptorin F presents a complex forming capacity similar to that of ebselen, whereas praeruptorins C and H outperformed the reference product. A representative molecular model of the praeruptorin C–DMT1 complex is shown in Figure 6. The drug fits well into the apical groove of the protein, positioning its tricyclic moiety in a narrow cleft, well accessible to the solvent. Several hydrogen bond interactions are implicated in the stability of the drug–protein complex, notably through the two arginine residues Arg149 and Arg153, and the tryptophan residue Trp505. A few additional van der Waals contacts and alkyl interactions contribute to the stability of the complex (Figure 6c). The amino acids involved in the complex are essentially the same as those responsible for the stability of the ebselen–DMT1 complex. The orientation of the two ligands within the binding site is a little distinct. The molecules partially overlap (Figure 7). The 10-isovaleryl chain of praeruptorin C is not implicated in the interaction whereas the 9-angeloyl side chain contributes importantly to the interaction, along with the dihydropyran unit. The isomeric orientation of the two 9–10 side chains seems to be an important structural element because praeruptorin E with a

9*S*,10*S* configuration binds less well to DMT1 than its isomer praeruptorin C with a 9*R*,10*R* configuration. Praeruptorin A presents the same 9*R*-angeloyl side chain as praeruptorin C and binds reasonably well to DMT1. In contrast, praeruptorin D with a 9*S*-angeloyl side chain is less efficient. Moreover, praeruptorin G lacking this angeloyl side chain is the weakest binder in the series. The secondary importance of the side chain at position 10 is illustrated with praeruptorin F which is an analog of praeruptorins B and D. Praeruptorin F can form binding complexes with DMT1 despite the absence of site chain at position 10. These observations reinforce the conclusion the side chain at position 9 and its configuration (9*R*) constitute a prime binding element.

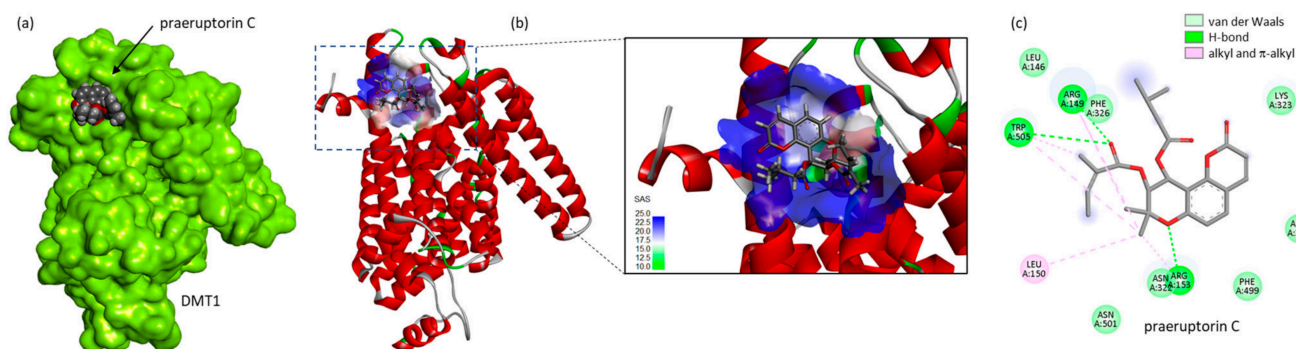


Figure 6. (a) Molecular model of praeruptorin C bound to DMT1. (b) A close-up view of praeruptorin C in its binding site, with the solvent-accessible surface (SAS) surrounding the drug binding zone (color code indicated). (c) Binding map contacts for praeruptorin C bound to DMT1 (color code indicated).

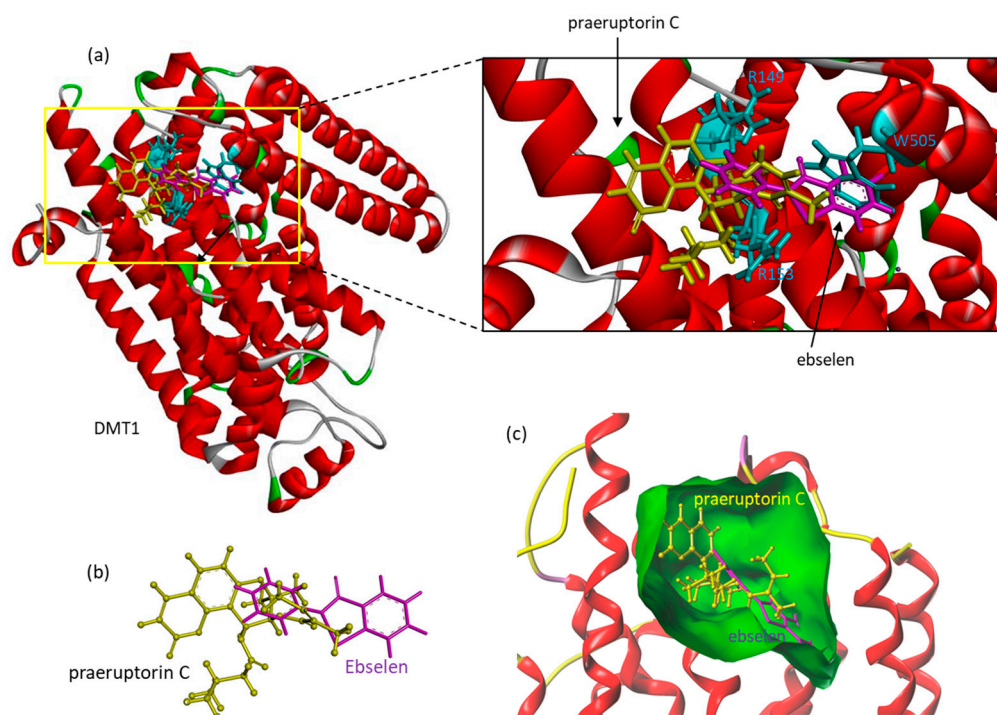


Figure 7. Comparison of the DMT1 binding orientation of praeruptorin C and ebselen. (a) Superimposed binding of the two ligands and a detailed view of the binding site, with the three important amino acids implicated in the protein–drug interaction (Arg149, Arg153, Trp505). (b) Overlapping models of praeruptorin C and ebselen in the binding site. (c) Another view of the protein cavity with the two bound ligands.

The structure-binding relationships are not necessarily straightforward. The atypical compound praeruptorin H displays a good DMT1 binding capacity despite the lack of an angeloyl side chain and a 9*S*-configuration. This compound was found to form binding complexes with DMT1, better than praeruptorin F and ebselen. But here again, the binding relies essentially on the protein interaction with the side chain (3-methylbutanoyloxy) at position 9, not at all the side chain (methylbutanoate) at position 10 (Figure 8). Therefore, it reinforces the conclusion that the drug side chain at position 9 represents a key binding element. Altogether, the analysis confirms the capacity of praeruptorins to bind to DMT1 and suggests that the best ligand in the series is praeruptorin C (in silico). This natural product is well shaped to interact with the transporter. The calculations with this compound gave a highly negative ΔE value and a satisfactory free energy of hydration (ΔG). For a given compound, ΔG describes the transfer of the small molecule between gas to water, hence the transfer of a molecular ligand from solution to a binding site in the case of a biomolecular binding interaction (solvation/desolvation) [53]. The data suggest that the transfer of praeruptorin C to its binding site can occur without energy penalty. In parallel, it is interesting to underline the good behavior of praeruptorin H which displays the highest ΔG values in the series, suggesting a facilitated transfer to the protein pocket.

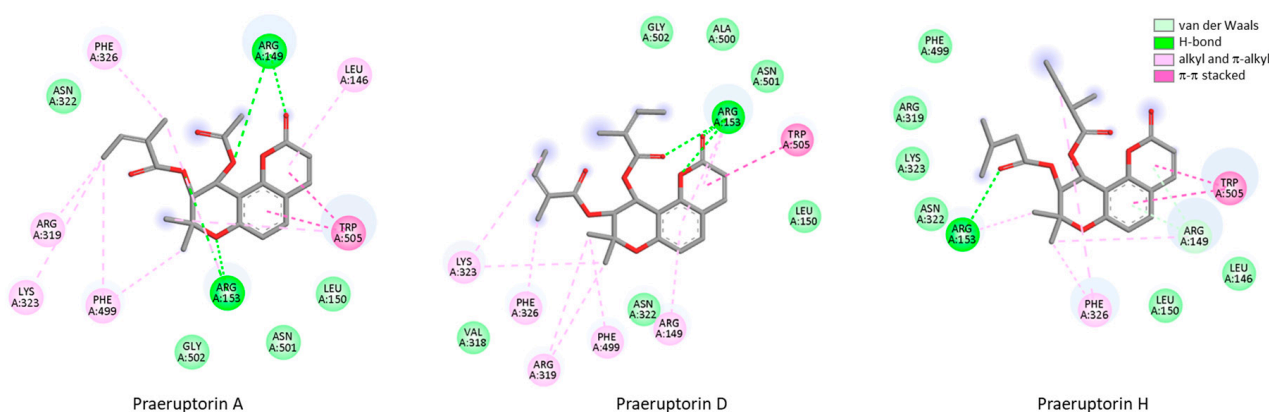


Figure 8. Binding map contacts for praeruptorins A, D, and H bound to DMT1 (color code indicated).

3.2. Binding of Qianhuocoumarins to DMT1

The above data suggesting that praeruptorin C displays a high affinity for DMT1 prompted us to look for analogous natural products susceptible to bind to the protein. The qianhuocoumarin series of molecules was selected (Figure 3). They represent a rarely studied group of natural products isolated from the root of *Peucedanum praeruptorum*. Their name derives from the Chinese Drug “Bai-Hua Qian-Hu”, the roots of *P. praeruptorum* [29,54]. Most of them are angular pyranocoumarin derivatives similar to the praeruptorins. The first three members in the series, qianhuocoumarins A-C, were isolated in 1993 [55,56] and the last member qianhuocoumarin J dates from 2010 [34]. The series includes two atypical, linear tricyclic molecules, qianhuocoumarin F and G [31] but the other ones are praeruptorin analogs (Figure 9). The compounds have been isolated and structurally characterized, but their pharmacology remains essentially unknown [57].

The same docking procedure was applied to study the binding of the 10 qianhuocoumarins (A-J) to DMT1 as for the praeruptorins. Each compound was positioned within the ebselen binding site and the best poses were determined through calculation of $\Delta E/\Delta G$ values (Table 1). The best two ligands in the series were qianhuocoumarins C and I which gave ΔE values equivalent to that measured with praeruptorin D. Qianhuocoumarin A is also a good ligand. Surprisingly, the other seven qianhuocoumarins were much less prone to bind to DMT1. Nevertheless, these compounds provided interesting support

the structure-binding relationships discussed above. The two linear derivatives, qianhuocoumarins F-G, are the weakest binders in the series. The angular scaffold (2-oxo-9,10-dihydropyrano[2,3-f]chromenyl) seems to be important for the target binding. The two good binders, qianhuocoumarins A and C, have no substituent at position 9 but the hydroxyl group has a favorable 9*R* configuration. However, the structure-binding relationships are not simple because the best binder in the series is qianhuocoumarin I which is equipped with a 9*S* acetyl group. This acetyl group is directly implicated in H-bond interaction with residue Arg149 of DMT1 whereas the adjacent angeloyl side chain plays no role in the protein interaction (Figure 9). Once again, this case illustrates the essential role of the 9-substituent in the protein interaction. Qianhuocoumarins A and I share a roughly similar orientation within the protein binding site with the convex side of the tricyclic chromophore inserted within the site. The two 9,10 substituents point on the concave side more open to the solvent or to interaction with other protein partners (Figure 9). Qianhuocoumarin I emerges as a good binder but it remains significantly inferior to the leader praeruptorin C, definitely the best DMT1 ligand identified in this study.

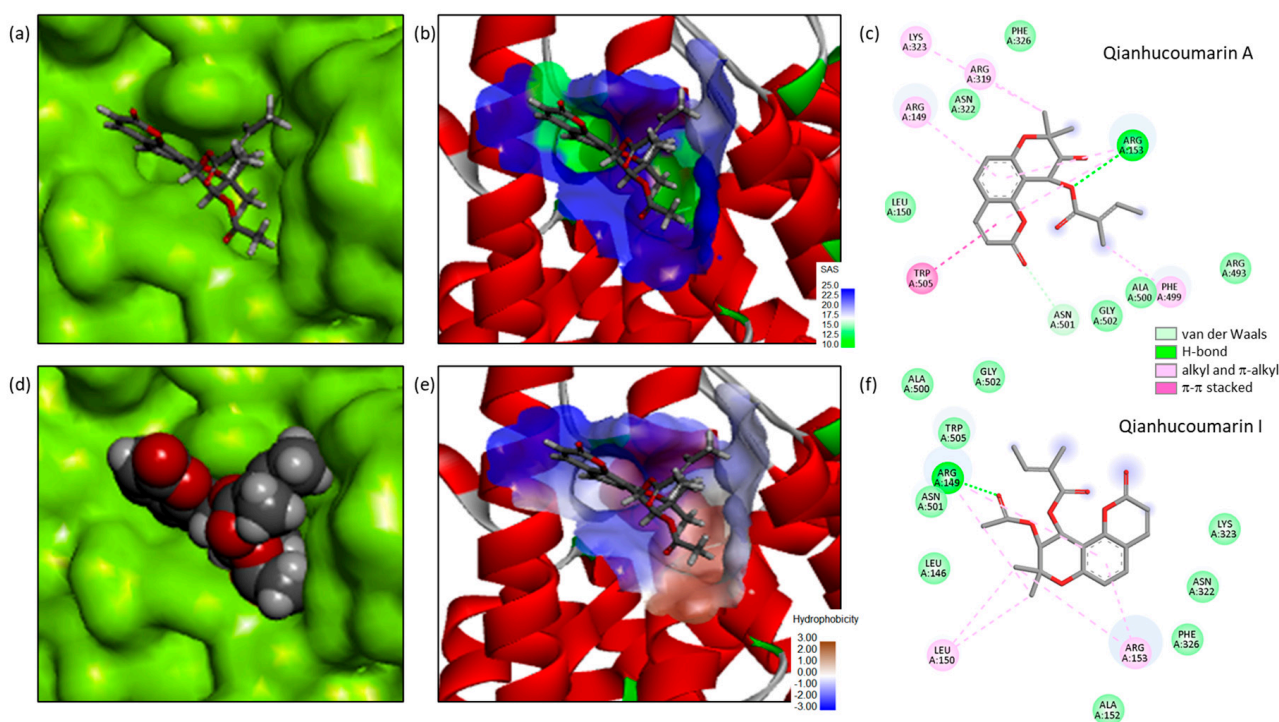


Figure 9. Binding of qianhuocoumarins A (top) and I (bottom) to DMT1. (a,d) Qianhuocoumarins A or I bound to DMT1. (b,e) A close-up view of the ligand in its binding site, with the solvent-accessible surface (SAS) or hydrophobicity surrounding the drug binding zone (color code indicated). (c,f) Binding map contacts for the two ligands.

4. Discussion

Inhibitors of the divalent metal transporter DMT1 (SLC11A2) are of interest to regulate cancer cell death mechanisms such as ferroptosis and to treat pathologies associated with an oxidative stress [5]. DMT1 plays essential roles in most cells, notably to control iron and manganese uptake in neurons [58–60]. Damages caused by DMT1-mediated iron overload have been implicated in pathologies associated with cartilage degeneration like osteoarthritis [5,61]. The upregulation of DMT1 is correlated with ferroptosis activation in osteoarthritis [62]. The expression of DMT1 is often increased in inflammatory pathologies, such as ulcerative colitis [63]. Therefore, it is of interest to identify small molecules regulators of DMT1-mediated metal transport.

In recent years, progresses have been made in the identification of small molecules DMT1 inhibitors [8,19,20]. Thus far, the archetypical DMT1 inhibitor remains the antioxidant drug ebselen which can bind to DMT1 to regulate its expression in cells, thereby regulating also the uptake of cellular iron [16,17]. Ebselen is an organoselenium drug candidate but it has multiple protein targets and mechanisms of action, notably through inhibition of thiol-containing proteins [64–66]. There is a need for more efficient and more selective inhibitor of DMT1. Along these lines, interesting data have been reported with the natural product praeruptorin A characterized as a DMT1 inhibitor in the frame of a high-throughput screening program aimed at identifying novel inhibitors of ferroptosis. The compound was found to reduce accumulation of Fe^{2+} ions and to inhibit ferroptosis in cardiomyocytes through neutralization of DMT1 [24]. This pioneer work provided the impetus for the analysis of the different praeruptorins to interact with DMT1 using molecular modeling. We knew there were eight praeruptorins as well as a diversity of related natural products, notably the qianhuocoumarin family. These natural products have been largely neglected thus far. It was a good opportunity to shed light on this group of natural substances isolated from the roots of the Chinese medicinal plant *Peucedanum praeruptorum* Dunn (Radix Peucedani [前胡], also known as Qian Hu) used to treat chronic bronchitis, asthma, pneumonia and other lung pathologies [28].

Praeruptorin A is known for its anti-inflammatory and anticancer properties and its capacity to inhibit ferroptosis [25,26,67,68]. Its congeners also present interesting pharmacological properties, including anti-inflammatory, anticancer, and immune-modulatory effects [69]. But thus far, investigations have been concerned essentially with praeruptorins A-C, not the other members like praeruptorins E-H discovered more recently. Here for the first time, all praeruptorins have been compared for their capacity to bind to DMT1 in silico. Several good binders were identified and structure-binding relationships were delineated. The discovery of new potential DMT1 binders prompted us to study the related products qianhuocoumarins A-J to broaden the SAR information.

It is important to recognize the caveats of this study based on a docking analysis of the drug–target interaction. There are several limitations, notably at the technical level. In this study, the protein is considered as an isolated free protein entity, not in its membrane environment with surrounding proteins partners. The conformational state of the DMT1 protein considered here (an occluded state) may incorrectly represents the protein organization and neglects its dynamic. The docking analysis has been performed to select potential DMT1 ligands. It is an in silico prioritization study via a preliminary analysis of protein–ligand interactions, not an analysis of the ligand effects on protein function. A deeper analysis, using notably molecular dynamics simulations in a membrane-relevant DMT1 model, will be needed to support the present observations. An experimental validation is also required to confirm ligand binding to the protein, the potential inhibition of the metal transport activity, and the resulting cellular effects (e.g., inhibition of $\text{Fe}^{2+}/\text{Mn}^{2+}$ transport, modulation of ferroptosis). These limitations are kept in mind and they call for caution against an overinterpretation of the in silico data which may lead to erroneous conclusions regarding the functional impact of the binding data. Despite these important limitations, the analysis is interesting to guide the selection of potential ligands.

The key point of the docking analysis is the identification of praeruptorin C as a robust DMT1 binder. Its capacity to form complexes with DMT1 is well superior to that of praeruptorin A. The observation is important because praeruptorin C is a well-characterized anticancer agent. The compound has shown antiproliferative and antimetastatic effects in lung cancer models [70], in addition to analgesic, neuroprotective, and anti-osteoporotic effects evidenced in murine models [71–73]. The molecular origin of these effects is not precisely known at present. A study has raised the hypothesis that

the compound could bind to the protein kinase PIK3, so as to block the PI3K/AKT/GSK3 β signaling pathway in the hippocampus of diabetic (T2DM) mice. The potential binding of praeruptorin C to PI3K was also inferred from a molecular modeling analysis [74]. The natural product can alter different pathways in cells. It is likely that it has different protein targets.

Praeruptorin C can bind well to the ebsele binding site on DMT1. The orientation of the two ligands within the binding zone is a little distinct, as illustrated in Figure 7. The curved tricyclic moiety of praeruptorin C occupies a relatively large zone in the binding domain and the attached side chains extend toward the wall of the binding cavity to interact with specific residues. This model can be used as a guide to identify other DMT1 ligands with an angular-type pyranocoumarin scaffold. There exist other products with a similar configuration, in particular in the khellactone series. Analogs of trans-3'-angeloylkhellactone (which is in fact praeruptorin F) have been reported [75]. Other coumarins with a related scaffold, including glycosylated angeloylkhellactone derivatives can be tested as potential DMT1 binders [76–78]. The present study opens novel perspective for the discovery of natural products targeting DMT1. Complementary studies are ongoing using khellactone and dihydroseselin derivatives. A large range of naturally occurring dihydroseselin is available and these products are accessible by chemical synthesis [79,80]. Hopefully, the study will encourage medicinal chemists to design new DMT1 inhibitors based on the coumarin scaffold of praeruptorins.

This work also shed light on qianhuocoumarins which have been little studied in recent years. These compounds were discovered in the mid-1990s [31–33,55,56,81] but their pharmacology is little known. One or two qianhuocoumarins have been identified regularly in *Peucedanum* species (e.g., *P. praeruptorum*, *P. decursivum*) [69,82–85]. Qianhuocoumarins C and I present a good affinity for DMT1 (at least in silico), almost equivalent to that of ebsele. They deserve further investigations, not only to evaluate their interaction with DMT1 but also to study their druggability through an evaluation of their ADMET properties and intrinsic molecular properties.

In conclusion, the molecular docking analysis confirms the capacity of praeruptorin A to bind to DMT1 and suggests that a few other praeruptorin derivatives display an equally good capacity to form complexes with the target protein. The in silico study identifies praeruptorin C as the best potential ligand in the series, with a DMT1-binding capacity possibly superior to that of praeruptorin A and the reference product ebsele. Some structure-binding relationships have been determined, notably with the testing of the related qianhuocoumarin series of natural products. The study paves the way to the discovery of other coumarin derivatives targeting the metal transporter DMT1 (SLC11A2).

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Abbreviations

The following abbreviations are used in this manuscript:

DMT1	Divalent Metal Transporter 1
MC	Monte Carlo
MD	Molecular Dynamics
MM	Molecular Mechanics
SLC11A2	Solute carrier family 11 member 2

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