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A Novel Bisphosphonate-Ligand Conjugate (NBLC) for Bone-Targeted Pb(II) Chelation and Suppression of Osteoclast-Mediated Bone Resorption

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Abstract

Introduction: Lead is a naturally occurring toxin which is prone to bioaccumulation in the human skeleton. Problematically, conventional chelating agents fail to acutely uptake lead – inadvertently targeting important divalent metal cations in the body (e.g., zinc) while primarily addressing only the plasma-bound toxins. For these reasons, this report aims to model a novel bisphosphonate-ligand conjugate (NBLC) which A. bears remarkable specificity for the bone, B. reduces bone-lead turnover into the blood via suppression of osteoclast activity mediated by Farnesyl Pyrophosphate Synthase (FPPS), and C. favorably complexes with lead amongst all other minerals in the body while depositing calcium in place of the uptaken metal.

Methods: The NBLC molecular model was designed on Marvinsketch and optimized in three-dimensional space for ligand-receptor docking using UCSF Chimera. The NBLC and other conventional bisphosphonates (Zoledronate and NE10575) were uploaded to Webina 1.0.4 to determine an average free energy (ΔG) and, subsequently, an average drug binding affinity (K_D) of the three most energetically stable FPPS-molecule complexes to gauge efficacy of the moieties as allosteric inhibitors. Thereafter, the average bond length of four coordinate covalent bonds between the bisphosphonates (including the NBLC) and two hydroxyapatite crystals was determined as a measure of molecular binding affinity to the bone.

Results: The NBLC achieved a K_D of 0.062 ± 0.003. By One-Way ANOVA, this result was statistically lower than the results obtained by the other FPPS-bisphosphonate complexes ($p = 2.59 \times 10^{-5}$), reinforcing that the NBLC is a more potent allosteric inhibitor of the osteoclast-mediating enzyme. Additionally, the average coordination bond length of the NBLC-hydroxyapatite complex was 3.13 ± 0.7Å, which, as determined via a two-tailed T-test, bore a statistically insignificant difference with the results obtained using Zoledronate ($p = 0.991$).

Discussion: The results demonstrate that the NBLC is capable of binding bone hydroxyapatite and allosterically inhibiting FPPS.

Conclusion: The collected data suggests that the NBLC successfully meets the first two criteria defined in the introduction. As per the final criterion, this paper paves way for future work in synthesis and characterization of the NBLC to experimentally determine the thermodynamic stability of its metal complexes and ascertain its ability to selectively uptake lead while depositing calcium.

Keywords: coordination chemistry; chelation therapy; lead intoxication; bone; molecular engineering; autodocking; drug development; FPPS; bisphosphonate; py-bcpe

Introduction

Background, Toxicokinetics, and Consequences of Consumed Lead

Lead is a naturally occurring toxin capable of adversely and irreversibly affecting multiple body systems. While well-documented in the literature, lead persists ubiquitously across multiple media and is thereby consumed on a routine basis. Namely, the metal may be uptaken via "the inhalation of particulates generated by the burning of lead-containing material", the inadvertent "ingest[ion] of lead-contaminated dust", and most problematically, its consumption in trace amounts when dissolved in purified drinking water [1, 2].

Bioaccumulation of lead in the human body is a phenomenon that occurs when plasma-bound lead displaces the calcium that constitutes crystalline hydroxyapatite coating the bone due to lead's comparatively greater binding affinity for the crystal matrix and the similarity in ionic radii between both Pb^{2+} and Ca^{2+} [3-7]. By consequence, the following displacement reaction will occur at an equilibrium where the product is favored due to greater stability:

$$Ca_5(PO_4)_3(OH)_{(s)} + nPb^{2+}_{(aq)} \rightleftharpoons Ca_{5-n}Pb_n(PO_4)_3(OH)_{(s)} + nCa^{2+}_{(aq)}$$

Where $\boldsymbol{n}$ is an integer number between 1 and 5.

DOI Link: https://doi.org/10.26685/urncst.418

About 80% of the human skeleton is composed of cortical bone which surrounds the marrow, and 70% of the cortical bone is composed of hydroxyapatite, providing plasma-bound lead with plentiful surface area for attack [8]. When plasma-bound Pb^{2+} and hydroxyapatite-locked lead reach equilibrium, the metal is absorbed into deep, trabecular bone cavities to become inert and therefore inaccessible for removal by conventional chelating agents [4, 8]. However, when osteoclast cells degrade the bone to remodel the bone matrix in a process known as resorption, bone mineral, such as this deep layer, trabecular inert lead, rises to the cortical bone surface to become labile and thus free for exchange in the blood plasma [5]. Effectively, the bone itself becomes a large, lead reservoir with blood being the medium for Pb^{2+} to attack vulnerable, soft-tissues organs (Figure 1). Namely, Pb^{2+} may penetrate the blood-brain barrier to cause irreversible damage to the central and peripheral nervous system [1]. Lead also tends to disrupt calcium-based homeostasis, and it may even bind to and deteriorate the tertiary structures of peptides with thiol-rich binding sites to disrupt important metabolic pathways [9]. In general, lead bound to hydroxyapatite crystals allows for rapid bioaccumulation in tissue beyond the bone matrix, and this has severely negative implications for a plethora of biological systems in the human body.

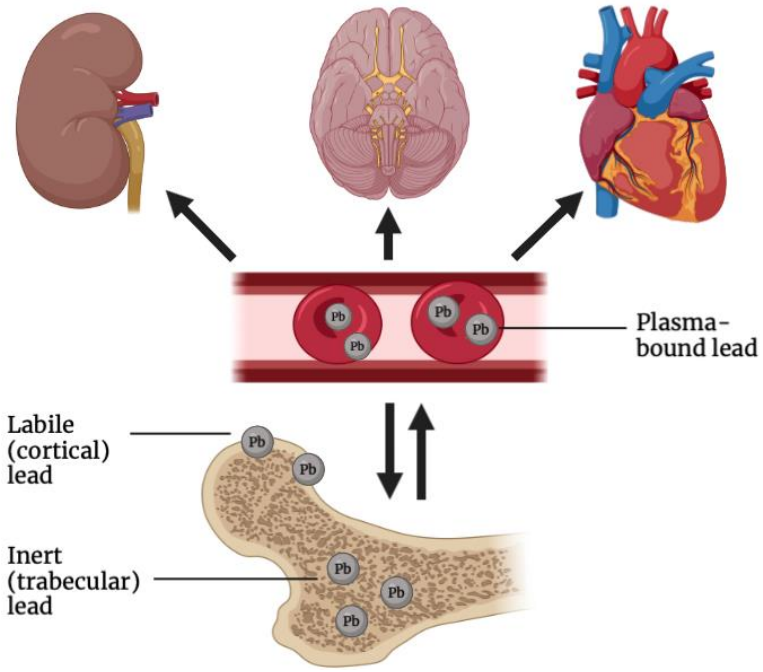

Figure 1. Toxicokinetics of Pb^{2+} described by its transfer between multiple biological systems, with the bone as a major reservoir. Drawn using BioRender.

For these reasons, it is no surprise that novel approaches to eliminate Pb^{2+} in consumables and in the environment are being developed at a rampant pace across literature, involving the use of media as creative as coffee grounds and processes as mechanical and rigorous as activated carbon-based Pb^{2+} adsorption, reverse osmosis, electrolysis, and cation exchange [2, 3]. Together, these emerging scientific approaches outline an agreed urgency to address the metal toxin in whatever form it may take. Though common among these reports is the finding that water can never be completely purified post-filtration, which means consumption of lead is invariable. This is problematic because lead is prone to bioaccumulating in the body, with upwards of a 30-year half-life, even at low exposure levels [4]. As a result, there is a strong impetus to develop and refine protocol for drug-mediated interference of consumed lead.

Chelating Agents: The Current Ailment for Mitigating Bodily Lead Concentrations

While the bone is the largest reservoir of lead accounting for over 75% of lead in children and 90% in adults, no such chelating agent in the literature has been manufactured for the selective targeting of bone-lead [6, 8, 10]. Ethylene-diaminetetraacetic acid (EDTA), for example, capably targets lead in soft tissues, but primarily fails to address the source bone-lead while secondarily depleting the body of important divalent cationic minerals such as zinc and copper [11, 12]. Further, it is also often found that even after administration of chelating agents designed to complex and uptake lead, concentrations rebound afterwards because bone resorption (via osteoclastic activity) release deep-layer lead, as earlier mentioned [13]. While not explicitly discussed in these reports, administration of chelating agents that interact with

hydroxyapatite-complexed lead may engender low-bone-density induced osteoporosis due to an inability to restore calcium in place of the chelated lead. For these reasons, current ailments for lead intoxication via known chelating agents are somewhat disadvantageous, creating an impetus for newer, efficacious molecular models.

Bisphosphonates as a Necessary Chemical Component

Bisphosphonates are analogues of pyrophosphates (Figure 2). This molecule is capable of binding strongly onto the bone because both of its flanking inorganic phosphate groups act as a monodentate ligand for hydroxyapatite, rendering a generalized bisphosphonate as an excellent structural component of any drug designed to selectively target the bone [14]. In addition, specific iterations of bisphosphonate which contain nitrogen in a heterocyclic ring have proven to be strong antiresorptive agents: moieties which inhibit osteoclastic activity and diminish bone resorption rates [15]. This antiresorptive mechanism occurs because nitrogen-containing bisphosphonates inhibit Farnesyl Pyrophosphate Synthase (FPPS), an enzyme which plays a key role in the Mevalonic Pathway responsible for mediating osteoclast activity. The implication of reduced osteoclast activity is decreased bone turnover rates, allowing for damage control by reducing the amount of already-accumulated deep-layer bone-lead from mobility back into the blood pool. Thus, this tendency of the (nitrogen-containing) bisphosphonate, in conjunction with its remarkable specificity for the bone, deems the molecule a necessary component for the drug to be developed in this paper.

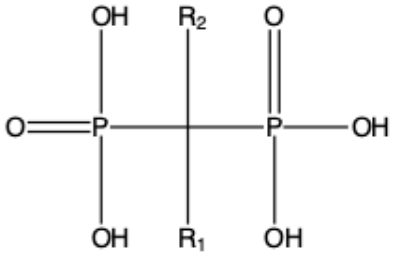

Figure 2. Generalized structure of bisphosphonates, where R groups are variable. Drawn using Marvinsketch.

Py-bcpe: A Ligand with Nitrogen-Containing Pyridyl Pendants

Py-bcpe is an octadentate ligand elucidated to complex with Ca^{2+}, and even more so with Pb^{2+}, among other divalent metal cations, with remarkable selectivity (Figure 3) [16]. Unlike conventional chelating agents, py-bcpe binds to the central metal at eight different coordinates. High metal-to-py-bcpe stability is also characterized by the ligand's ability to form five-membered chelate rings, while additionally containing four pyridyl units with a total of six nitrogen electron donors stabilizing the metal center via dative bonds in conjunction with the two deprotonated oxygen groups on the flanking carboxylate anions. For these reasons, py-bcpe is an excellent candidate as a ligand component to the lead-uptaking molecular model which was developed in this paper.

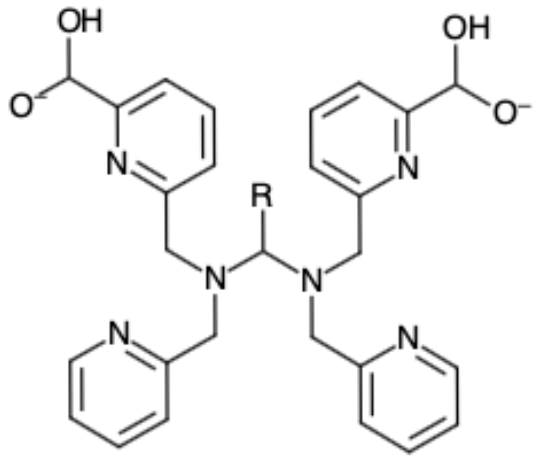

Figure 3. The generalized structure of the py-bcpe ligand. Drawn using Marvinsketch.

The NBLC: Proposing a Novel Molecular Model

To address the need for a molecular model capable of safely targeting bone-lead without the risk of diminishing bone-density, and one which further prevents deep-layer, trabecular, inert lead from mobilizing back into the blood plasma, the Novel Bisphosphonate-Ligand Conjugate (NBLC) was developed (Figure 4). Unlike conventional chelating agents, the molecule uses a bisphosphonate "warhead" to bind strongly onto cortical hydroxyapatite, thereby allowing the conjugated py-bcpe ligand to selectively chelate lead found at the cortical bone surface. Because the py-bcpe ligand contains nitrogen groups contained in heterocyclic rings (i.e., contains four pyridyl units), the NBLC should also take on the antiresorptive properties of a conventional nitrogen-containing bisphosphonate, allosterically inhibiting FPPS, leading to osteoclast apoptosis, and therefore reduced bone-lead turnover rates.

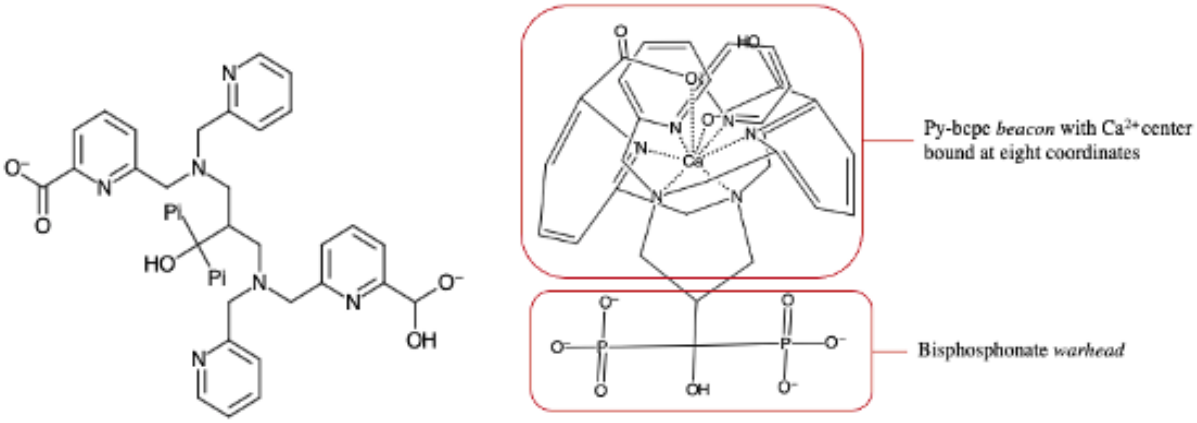

Figure 4. The NBLC without a central Ca^{2+} metal, where Pi denotes an inorganic phosphate group (*left*) and the NBLC in the intended form, with a central Ca^{2+} metal (*right*). The bisphosphonate segment of the molecule acts as the "warhead" binding onto bone hydroxyapatite, and the py-bcpe ligand acts as the "beacon" which chelates Pb^{2+} and releases a Ca^{2+} ion in its place. Drawn using Marvinsketch.

Objectives of the NBLC

To summarize, the NBLC has three main objectives (addressing the limitations of conventional chelating agents), each of which will be measured in this paper:

1. Bear remarkable binding affinity for hydroxyapatite to promote selective lead chelation on the bone.
2. Capability to adopt the antiresorptive properties of nitrogen-containing bisphosphonates by readily binding onto FPPS to subsequently reduce bone-lead turnover rates, thereby minimizing the amount of deep-layer inert lead from becoming labile and tracing back into the blood.
3. Contain a chelating agent which can accommodate a central calcium ion capable of displacing labile lead complexed to hydroxyapatite on cortical bone surfaces; in this way, there is consideration for calcium restoration of the bone at the expense of uptaken lead.

Mechanism of Attack by the NBLC

The intended mechanism of the NBLC in the bone is diagrammed in Figure 5, with its steps being detailed as follows:

1. The administered NBLC-Ca^{2+} complex in the blood plasma uses it bisphosphonate warhead to latch onto hydroxyapatite coating the outermost cortical bone. Here, the NBLC chelates lead stored as $Pb_5(PO_4)_3(OH)$ to form an NBLC-Pb^{2+} complex; the uptaken Pb^{2+} is replaced by a released Ca^{2+} ion to maintain the crystalline hydroxyapatite, $Ca_5(PO_4)_3(OH)$, and subsequently, bone density. This reaction is depicted in Figure 6.
2. A) The NBLC-Pb^{2+} complex is absorbed by the bone matrix, where it proceeds to allosterically inhibit FPPS, leading to osteoclast apoptosis, and reduced bone resorption rates.

   B) Alternatively, the NBLC-Pb^{2+} complex immediately detaches from the cortical hydroxyapatite, retracing back into the blood plasma to be excreted.
3. The NBLC-Pb^{2+} complex is released from FPPS, and by (slower) resorption of the bone rises to the cortical bone surface.
4. The NBLC-Pb^{2+} complex is released back into the blood plasma, tracing into the excretory system, and is removed from the body.

In addition, the following lettered arrows of Figure 5 are worth noting:

A. Arrow denotes Pb^{2+} ions (as well as Ca^{2+} ions) binding onto bone hydroxyapatite. Localized cavities of lead begin to form on the bone.
B. Arrow denotes movement of minerals via absorption by the bone. Note that it is by absorption that labile lead in the cortical bone sinks into the deeper-layer trabecular bone to become inert, where it is stored as $Pb_5(PO_4)_3(OH)$.
C. Arrow denotes movement of minerals via resorption by the bone. Note that it is by resorption that inert lead in the trabecular bone may rise to the cortical bone surface to become labile and thus capable of exchange back into the blood plasma. This arrow is dotted because following *step 3* where FPPS is inhibited by the NBLC-Pb^{2+} complex, resorption rates are dramatically reduced so that inert lead in the trabecular bone is discouraged from mobilizing to cortical tissue and becoming labile.
D. Arrow denotes efflux of minerals (Ca^{2+} and Pb^{2+}) from the trabecular bone surface back into the blood plasma; both ions may trace through the circulatory system to attack other organs or biological systems in the body.

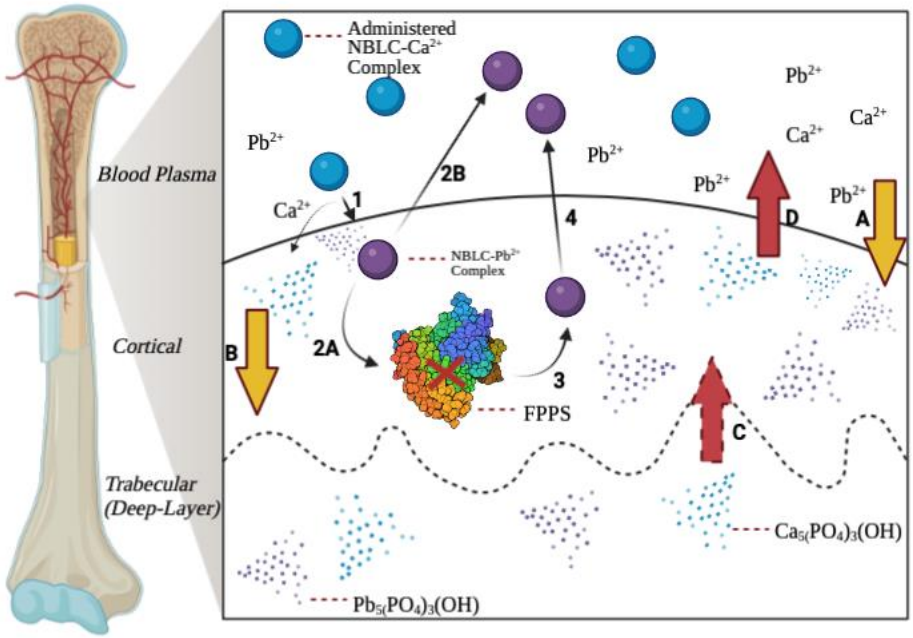

Figure 5. Mechanism of attack by NBLC within the bone matrix, with labelled steps. Drawn using BioRender.

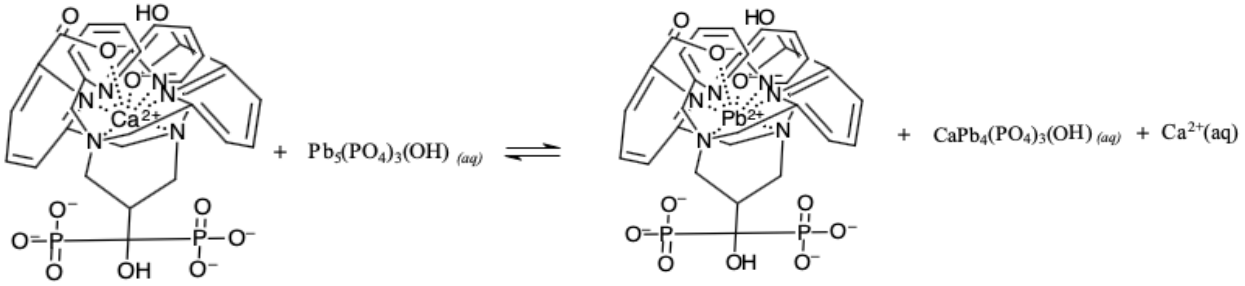

Figure 6. Chelation of lead by NBLC, and consequent release of a Ca^{2+} ion. Drawn using Marvinsketch.

Methods

Synthesis of the NBLC

A synthetic route for the NBLC was determined using Sci-Finder N: a program which can yield reaction pathways using retrosynthesis (Figure 7). Retrosynthesis was employed to determine the most efficient, cost-effective pathway for the synthesis of the NBLC by drawing on a comprehensive database of synthetic protocols for analogous chemical precursors.

Determining Efficacy of FPPS Inhibition by the NBLC via Autodocking

Molecular docking is a process used to describe how a ligand (i.e., the NBLC) interacts with a target protein (i.e., FPPS), determining their mutual binding orientation and binding affinities (in J/mol), both of which are apt measures to determine how appropriate a molecule may perform as an enzymatic inhibitor. Thus, capability of NBLC as an allosteric inhibitor of FPPS relative to known nitrogen-containing bisphosphonates (Zoledronate and NE10575, as pictured in Figure 8) will be measured using a combination of docking software, namely, UCSF Chimera and Webina 1.0.3 by Durrant Labs.

The NBLC, along with Zoledronate and NE10575 were rendered on Chimera, and their structures were minimized (a process which yields the most energetically stable conformation of a molecule; this is the form to be used for docking) (Figure 9). These were then uploaded to Webina 1.0.3.

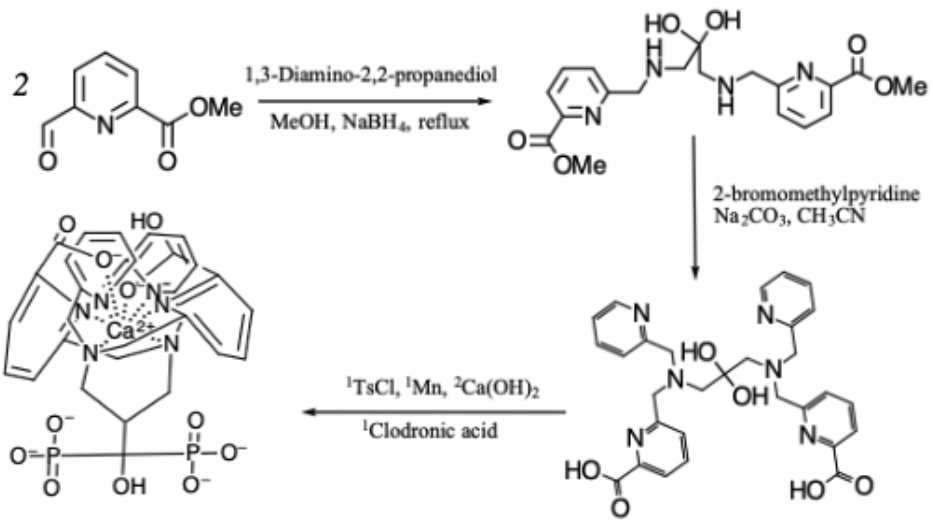

Figure 7. Synthetic pathway of the NBLC, where superscripts denote the order in which reagents are applied. Drawn using Marvinsketch.

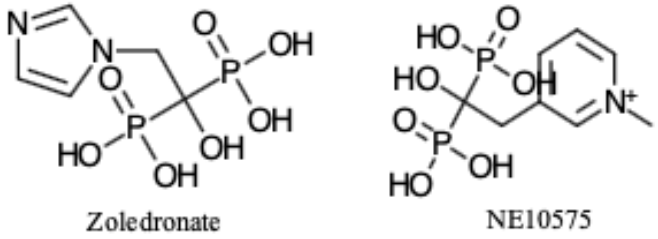

Figure 8. Structure of Zoledronate and NE10575. Drawn using Marvinsketch.

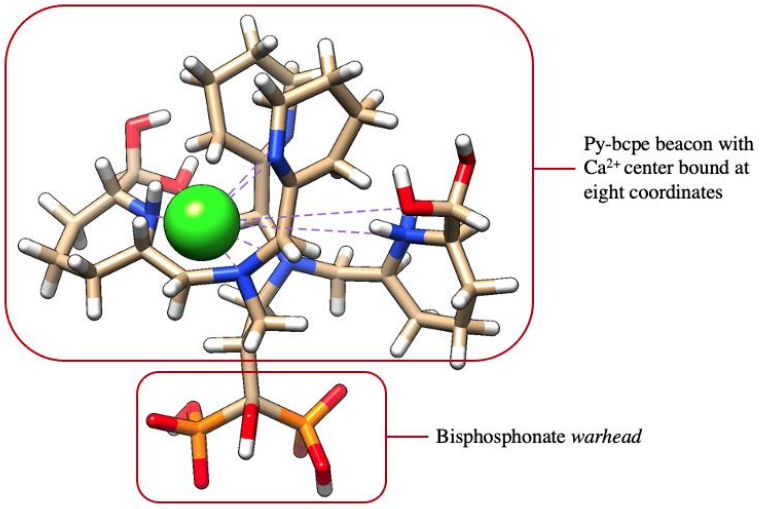

Figure 9. Minimized structure of the NBLC, as rendered on UCSF Chimera, with labels. The same protocol was applied to Zoledronate and NE10575.

Furthermore, a PDB format of FPPS was obtained from RCSB PDB. The FPPS used in this paper can be identified as *2F7M: the crystal structure of unliganded human FPPS*. Thereafter, FPPS 2F7M was uploaded to Webina 1.0.3 as the target protein.

Individually, Webina 1.0.3 generated the binding affinity ΔG (J/mol) of every ligand-FPPS complex (the NBLC-FPPS, Zoledronate-FPPS, and NE10575-FPPS) for multiple modes of orientation (Figure 10). To do this, Webina 1.0.3 uses an exhaustive energy-scoring function (a molecular mechanics model) to output probable mechanical interpretations for how a ligand docks onto a protein; of these interpretations, the most energetically favorable is determined through a stochastic global optimization approach to find a minimum in the sum of intermolecular and intramolecular interactions between and within the protein-ligand complex, which ultimately corresponds to a minimum in ΔG [16, 17]. For brevity in this paper, only the average ΔG of the three most energetically stable ligand-FPPS interactions was considered for each ligand-FPPS complex.

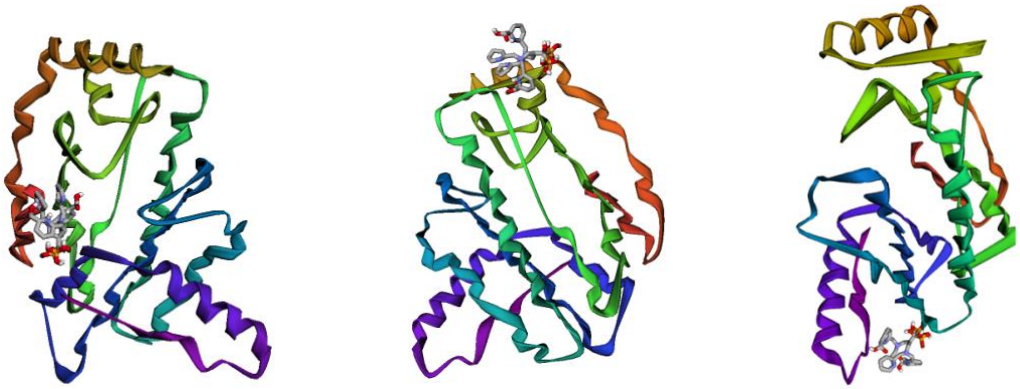

Figure 10. The three most energetically stable binding modes of the FPPS-NBLC complex, as rendered on Webina 1.0.3. The same complexes were obtained for Zoledronate and NE10575.

The obtained average $\boldsymbol{\Delta G}$ was then used to calculate the average drug dissociation equilibrium constant $\boldsymbol{K_B}$ – a unitless value – which describes the following equilibrium:

$$FPPS + NBLC \rightleftharpoons FPPS - NBLC$$

To calculate $\boldsymbol{K_B}$, the below thermodynamic equation was permuted:

$$\Delta G = -RTlnK_D \rightarrow K_D = e^{\frac{\Delta G}{-RT}}$$

Where $R = 8.314\, J/molK$ and $T = 298K$, assuming standard temperature and pressures hold.
Finally, the drug binding affinity constant K_D was derived using the following relation:

$$K_D = \frac{1}{K_B}$$

Determining the Binding Affinity of the NBLC for Bone Hydroxyapatite

To determine how capably the NBLC can bind on bone hydroxyapatite, an NBLC-hydroxyapatite complex was drawn on Marvinsketch and rendered on Chimera (Figure 11). The coordination bonds between the NBLC inorganic phosphate groups and the hydroxyapatite molecules were measured (in Angstroms), where shorter coordination bonds denote greater strength, and consequently, greater binding affinity. For contextualization, the coordination bond lengths of the NBLC-hydroxyapatite complex will be compared to those in the complexes other bisphosphonates (i.e., Zoledronate and NE10575) form with hydroxyapatite.

Analysis by One-Way ANOVA conducted across all three ligand-FPPS complexes yielded $p = 2.59 \times 10^{-5}$, revealing that a statistically significant difference existed between the drug binding affinity results of at least one ligand-FPPS pair. A subsequent two-tailed T-test (assuming equal variances) between the results obtained for the NBLC and Zoledronate yielded $p = 0.00102$ which reinforced a statistically significant difference. The same analysis for the results obtained by the NBLC and NE10575 yielded $p = 2.47 \times 10^{-4}$, reinforcing another statistically significant difference.

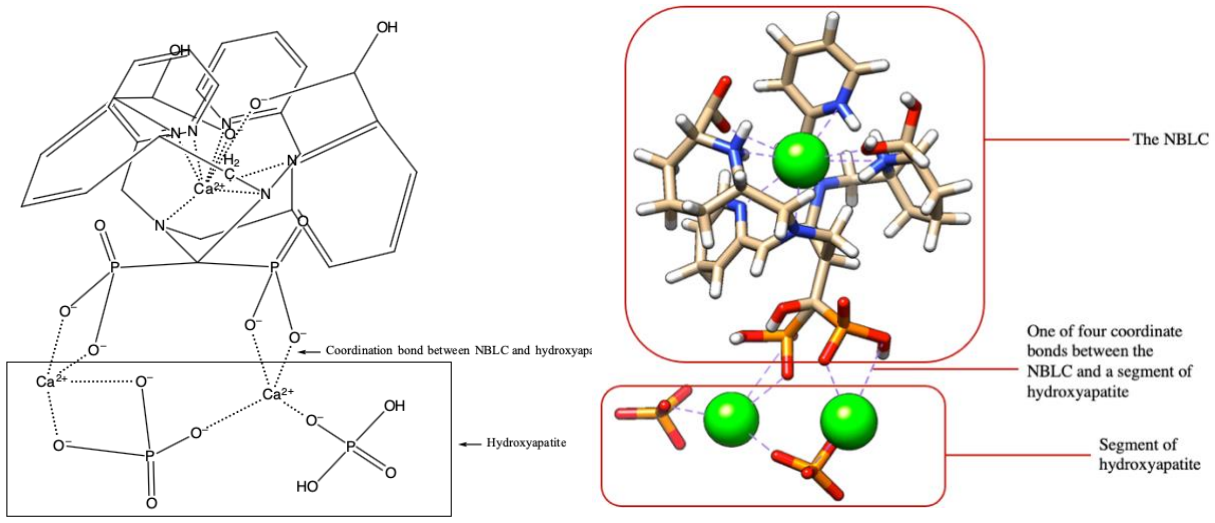

Figure 11. Coordination of the NBLC to hydroxyapatite, where dotted lines represent coordination bonds. Shorter coordination bonds indicate greater affinity between the NBLC and hydroxyapatite. The leftmost image was drawn on Marvinsketch, and subsequently rendered in UCSF Chimera on the right.

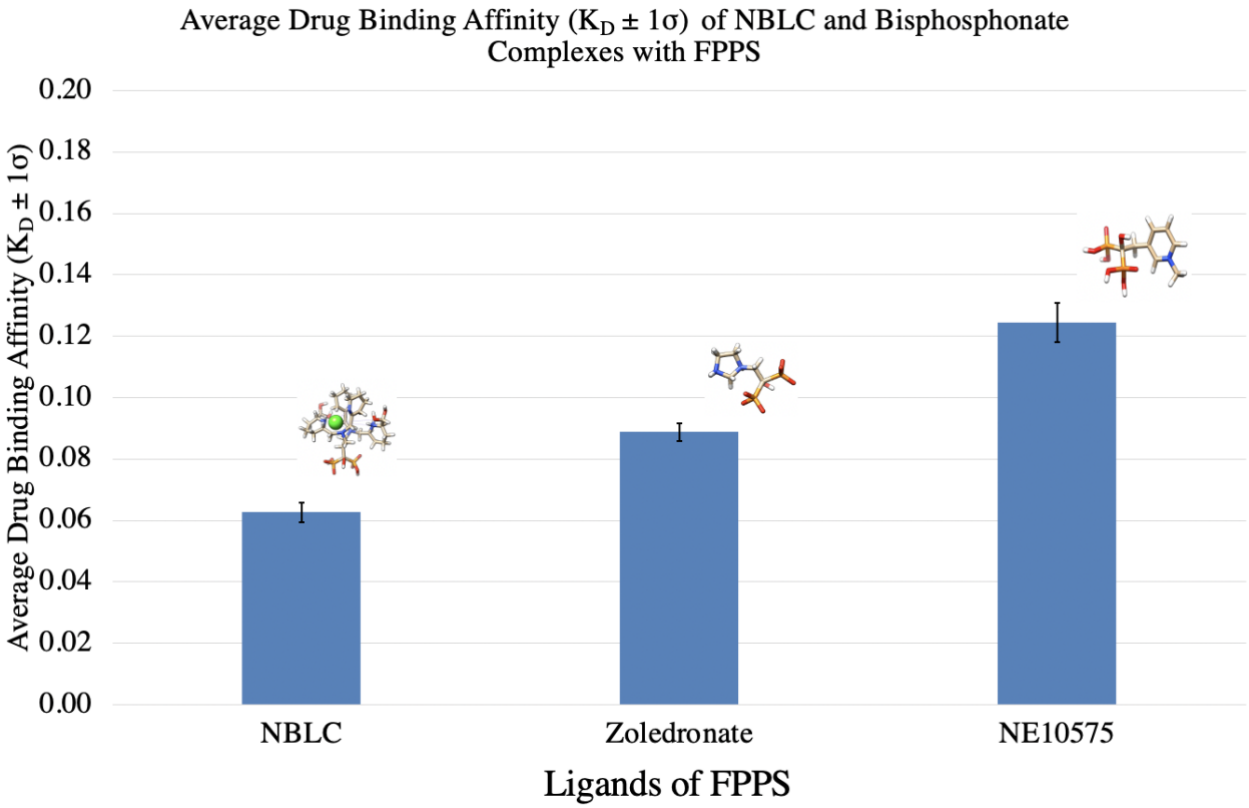

Figure 12. Average drug binding affinity (K_D) of the NBLC, Zoledronate, and NE10575 when complexed with FPPS. Created using Microsoft Excel.

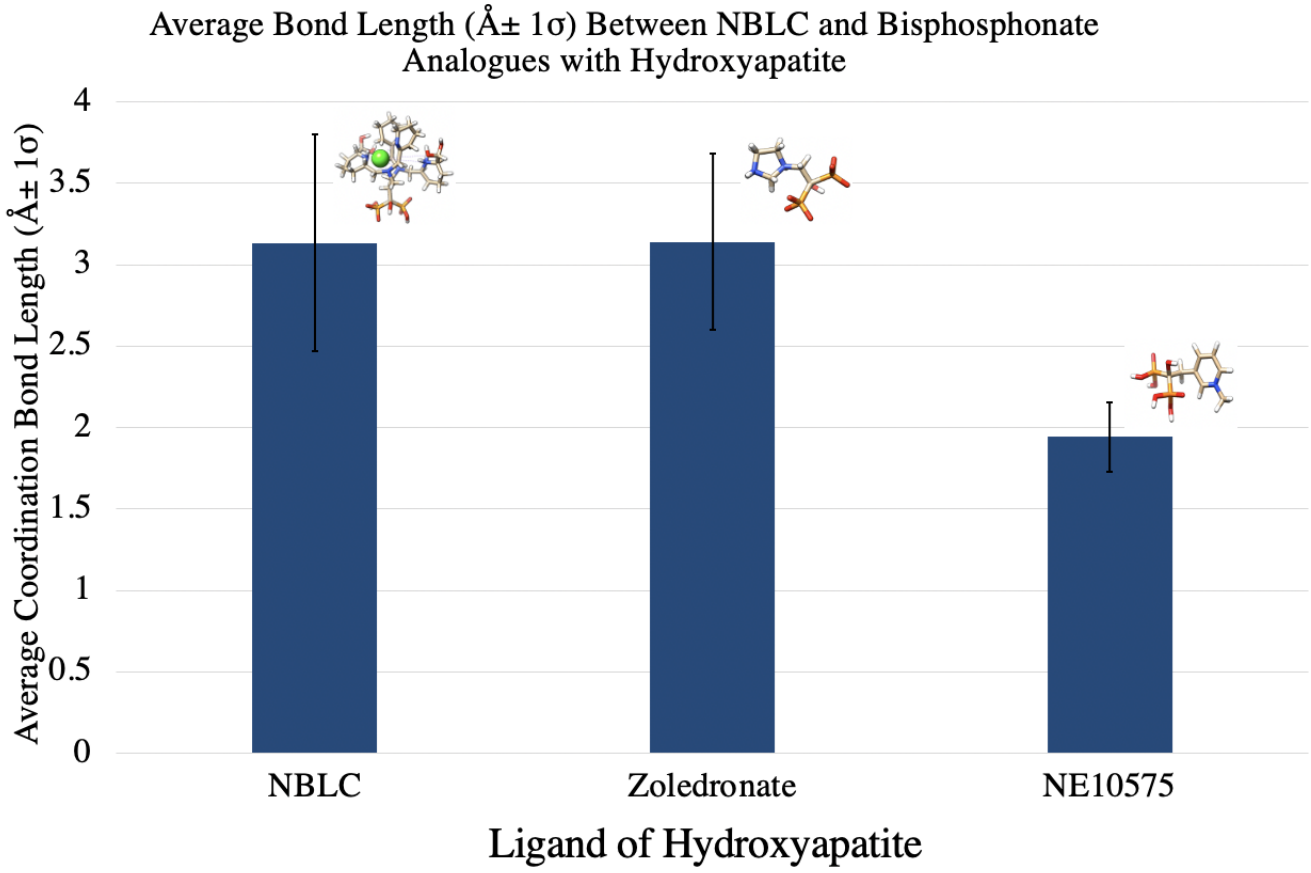

Figure 13. Average coordination bond lengths (Å) of the NBLC, Zoledronate, and NE10575 when bound to hydroxyapatite. Created using Microsoft Excel.

Results

Analysis by One-Way ANOVA conducted across all three ligand-hydroxyapatite complexes yielded $p = 0.0259$, revealing that a statistically significant difference existed between the bond-length results of at least one ligand-hydroxyapatite pair. A subsequent two-tailed T-test (assuming equal variances) between the results obtained for the NBLC and Zoledronate yielded $p = 0.991$ which reinforced a statistically insignificant difference, while the same analysis for the results obtained by the NBLC and NE10575 yielded $p = 0.0145$, reinforcing a statistically significant difference.

Table 1. Summary of Ligand-FPPS K_D Data and Ligand-Hydroxyapatite Bond Length Data ($\pm 1\sigma$). One-Way ANOVA and T-test (against the NBLC data) $p - values$ are provided, where $S =$ Significant Difference and $NS =$ Non-Significant Difference

Ligand	**Ligand-FPPS (K_D)**	**One-Way ANOVA $p - value$ (S/NS?)**	**T-test $p - value$ with the NBLC Data (S/NS?)**	**Ligand-Hydroxyapatite bond length (Å)**	**One-Way ANOVA $p - value$ (S/NS?)**	**T-test $p - value$ with the NBLC Data (S/NS?)**
The NBLC	0.062 ± 0.003	2.59×10^{-5} (S)	$- - -$	3.13 ± 0.7	0.0258 (S)	$- - -$
Zoledronate	0.088 ± 0.003		1.02×10^{-3} (S)	3.14 ± 0.5		0.991 (NS)
NE10575	0.12 ± 0.006		2.47×10^{-4} (S)	1.94 ± 0.2		0.0145 (S)

Discussion

Affinity for Bone Hydroxyapatite

Data in Figure 12 reveals that the average coordination bond length between hydroxyapatite and NE10575 is the shortest (1.94 ± 0.21Å), followed by the same complex with Zoledronate (3.14 ± 0.54Å), and lastly, the complex with the NBLC (3.13 ± 0.69Å). The statistically insignificant difference ($p = 0.991$) between the coordination bond lengths of both Zoledronate and the NBLC when complexed to hydroxyapatite – as established by One-Way ANOVA and a subsequent T-test – suggests that both moieties bind the crystal with similar affinity, assuming bond length is correlated to bond strength (i.e., shorter bonds are much stronger than longer bonds). Since Zoledronate is a potent bisphosphonate with remarkable bone specificity, the NBLC should follow suit, effectively proving its promise as a bone-targeting lead chelator, albeit not forming the shortest bonds (and thus the strongest bonds) with hydroxyapatite.

Affinity for FPPS

Data in Figure 13 reveals that the average K_D between FPPS and the NBLC is the lowest (0.062 ± 0.003), followed by the same complex with Zoledronate (0.088 ± 0.003), and lastly, the complex with NE10575 (0.12 ± 0.006). It was proven by One-Way ANOVA and subsequent T-tests that the NBLC-FPPS complex's obtained K_D value was significantly lower than the analogous complexes involving Zoledronate and NE10575 ($p = 1.02 \times 10^{-3}$ and $p = 2.47 \times 10^{-4}$ respectively). A lower K_D value indicates a greater K_B value, which in turn indicates that more FPPS-ligand complexes exist in solution at equilibrium. Thus, on the basis of K_D values, there would be far more FPPS-NBLC complexes than there would be FPPS-Zoledronate or FPPS-NE10575 complexes, at equilibrium. These results demonstrate that the NBLC is a far more potent inhibitor of FPPS than either of the two bisphosphonates. This provides basis for the idea that the NBLC capably inhibits osteoclast activity, and by consequence, suppresses bone resorption and reduces bone-lead efflux into the blood.

Metal Selectivity of the NBLC

The data provided in this paper does not foreclose the NBLC beacon (i.e., py-bcpe)'s ability to bind lead with greater preferentiality than other known chelating agents. However, research by Martinez et al. into the py-bcpe ligand reinforces that lead and calcium captured in a py-bcpe-metal complex is significantly more stable than analogous complexes with other known chelating agents (bcpe, bcpc, and EDTA), as determined via a pH-potentiometry method [16], rendering the NBLC a superior drug candidate. In addition, it was also reinforced that the py-bcpe-Pb^{2+} complex is more stable than the py-bcpe-Ca^{2+} complex, providing stronghold for the feasibility of a calcium-depositing and lead-uptaking mechanism via the NBLC.

Conclusions

In conclusion, the computationally modelled NBLC – having been compared to other known bisphosphonates (i.e., Zoledronate and NE10575) – has proven both its specificity for bone hydroxyapatite and potential for reduced bone-lead efflux into the blood. However, these results only satisfy two of the three original engineering goals. To gauge how effectively the NBLC can chelate lead in place of its coordinated calcium center, future work must entail synthesis, characterization, and metabolism of the molecule, followed by experimentally determined thermodynamic stability constants of its lead and calcium complexes.

Lead intoxication continues to necessitate more selective protocol to chelation therapy. The proactive work conducted in the development of the NBLC prods at the idea of tailoring selectivity of chelating agents by conjugating them to a delivery molecule while also doubling as an inhibitor to bodily activity which promotes proliferation of toxins from their source of accumulation. While the NBLC was designed to target bone-lead, the idea of manufacturing a molecule with a "warhead" and "beacon" component can theoretically give rise to a plethora of molecular models that chelate different toxins localized in selective parts of the human body. Hopefully, the research conducted in this paper can pave way for the development of conjugated chelating agents which optimize specificity and prevent mobility of toxic metals from their biological sources.

List of Abbreviations Used

NBLC: novel bisphosphonate-ligand conjugate
FPPS: farnesyl pyrophosphate synthase
EDTA: ethylenediaminetetraacetic acid

Conflicts of Interest

The author declares no conflict of interest within the curated body of work.

Ethics Approval and/or Participant Consent

No component of the research conducted warrants ethics approval or participant consent.

Authors' Contributions

MA: Modelled the NBLC, performed computational experiments to gather data, interpreted and analyzed said data, and created the manuscript. The entire body of work was developed by a single author.

Acknowledgements

The author would like to thank UBC's Multidisciplinary Undergraduate Research Conference for creating an opportunity to conduct and present research for an audience of students and professors while recommending the URNCST Journal as an additional outlet for publishing. The author would also like to thank Madhureeta Das Gupta for her unconditional support as an academic mentor.

Funding
This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Fatima Santillan, Amy Yeung, Jiachong Chu, Marie-Chloé Michaud Paradis
Article Dates: Received Aug 07 22; Accepted Jan 10 23; Published Mar 13 23

Citation
Please cite this article as follows:
Al-Seragi M. A novel bisphosphonate-ligand conjugate (NBLC) for bone-targeted Pb(II) chelation and suppression of osteoclast-mediated bone resorption. URNCST Journal. 2023 Mar 13: 7(3).
https://urncst.com/index.php/urncst/article/view/418
DOI Link: https://doi.org/10.26685/urncst.418

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