2018

ELUCIDATION THE TOXICITY MECHANISM OF ZINC OXIDE NANOPARTICLE USING MOLECULAR DOCKING APPROACH WITH PROTEINS

Krishna Pal Singh
Anupam Dhasmana
The University of Texas Rio Grande Valley
Qamar Rahman

Follow this and additional works at: https://scholarworks.utrgv.edu/som_pub

Part of the Medicine and Health Sciences Commons

Recommended Citation
Singh, Krishna Pal; Dhasmana, Anupam; and Rahman, Qamar, "ELUCIDATION THE TOXICITY MECHANISM OF ZINC OXIDE NANOPARTICLE USING MOLECULAR DOCKING APPROACH WITH PROTEINS" (2018). School of Medicine Publications and Presentations. 156. https://scholarworks.utrgv.edu/som_pub/156

This Article is brought to you for free and open access by the School of Medicine at ScholarWorks @ UTRGV. It has been accepted for inclusion in School of Medicine Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.
ELUCIDATION THE TOXICITY MECHANISM OF ZINC OXIDE NANOPIRICLE USING MOLECULAR DOCKING APPROACH WITH PROTEINS

KRISHNA PAL SINGH1, ANUPAM DHASMANA2, QAMAR RAHMAN1

1Department of Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India. 2Department of Himalayan, School of Biosciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India. Email: krishnapalsingh22@gmail.com

Received: 01 November 2017, Revised and Accepted: 04 December 2017

ABSTRACT

Objective: At present, toxicological tests are resource-intensive, time-consuming and require a large pool of animal models for toxicity assessment. To speed up the toxicity evaluation and to reduce animal suffering during toxicity assessment, the use of alternative methods including computational models is in high demand. The computational toxicity prediction methods are very helpful for the regulatory bodies to quickly assess the health impact of nanomaterial materials. In the present work, we have examined the mechanism of zinc oxide nanoparticle (ZnO-NP) proteins interaction and their effect of surface chemistries of ZnO-NP on the bioactive conformation of chemokines and other cytological proteins using in silico molecular docking approaches.

Methods: Molecular docking study was conducted using AutoDock 4.0 version and the visualization result using Discover Studio 4.0.

Results: In the present study, we observed that ZnO-NP has high binding affinity with the mitogen-activated protein kinases (P-38), nuclear factor kappa-light-chain-enhancer of activated B cell (NF-kB) proteins, and matrix metallopeptidase-9 with docking energies −8.81, −7.64, and −7.27 Kcal/Mol, respectively, involving with hydrogen, metal acceptor, and electrostatic interaction. The top interacting amino acid residues with ZnO-NP are GLY, PHC, ARG, ASP GLN and ASN.

Conclusion: Thus, based on the molecular docking studies, we determine that the ZnO-NP is strongly interacting with the chemokines and other cytological proteins thus responsible for blocking of the activation stimuli for these proteins to initiate the biological signals for the proper functioning. We have also extracted the information of interaction pattern of ZnO-NP with the surface-enriched amino acid residues of chemokine and cytological proteins using molecular docking approach.

Keywords: Zinc oxide nanoparticle, Molecular docking, Nanoparticle-protein interaction, Toxicity.

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i3.23384

INTRODUCTION

Nanomaterials are of great interest because of their novel properties, including a large specific surface area and high reaction activity [1,2]. In current scenario, expansion in nanotechnology engineering has increased the prompt development of many applications for nanomaterials such as metal nanoparticles (NP) (e.g., gold and silver), metal oxide NP (e.g., CuO, TiO2, and zinc oxide NP [ZnO]), C60 fullerenes nanocrystals, and carbon nanotubes (CNTs) [3-6]. In case of NP, the diverse materials were found, for example, gold, silica, titanium, CNTs, zinc, and quantum dots have shown unique mechanisms of proteins modifications, lipid peroxidation, and DNA fragmentation reactive oxygen species possible that lead to cellular damage and other several disorders including cancer [7]. ZnO is most widely commonly utilized as a group of nanomaterials [8]. The progressive utilized ZnO-NPs in sunscreens, biosensors, food additives, pigments, rubber manufacture, and electronic materials. Rise concerns have also been its unintentional health, environmental impacts, and negative effects on the survival and growth of organisms [9]. A number of in vitro studies proved that ZnO-NPs are toxic for mammalian cells and are even more toxic than other nanoscale structures of metallic oxide [10,11]. The interaction of nanomaterial with proteins results in physiological changes that lead to various pathological phenotypes. However, the mechanism underlying these changes remain poorly understood. In this study, we have selected some of the chemokine and cytological proteins which were previously suggested to interact with ZnO-NP in various experimental settings [12-16]. It was experimentally verified that the interaction of ZnO-NP with ICAM-1, IL8, IL1B, P-38, and nuclear factor (NF-kB) induces expression of these proteins [12,17-19], similarly in case of CCL18 and CD35, interaction resulted in decreased expression [14,20]. The matrix metalloprotease-9 (MMP-9) interacts with ZnO-NP which results in the increase enzymatic activity [14]. ZnO-NPs get absorbed systemically in the liver, adipose, and pancreas, which can elevate the level of zinc in the body [21]. The stimulation of oxidative stress is the vital part of the cytotoxicity of ZnO-NPs [22]. The major challenge in the current study is to deal with the size, density, and surface property variation of the nanomaterial because in the case of in vitro and in vivo experimental settings, these parameters were either poorly determined or with very broad range [23]. Furthermore, very few methods and studies are available where the toxicity of ZnO-NP was assessed using a computational method. In the case of new materials, computational toxicity prediction methods are now frequently used by regulatory bodies to quickly assess the health hazards. In the present study, we have investigated the mechanism of ZnO-NP-protein interaction and their effect of surface chemistries of ZnO-NP on the bioactive conformation of chemokines and other cytological proteins using in silico molecular docking approaches. We have selected those proteins which have already reported interaction with ZnO-NP and also well-established in the earlier works using in silico techniques, and the in-silico results have been discussed comparatively. We have specifically investigated the effect of NP toxicity and an insight into the regularity of interaction has been attempted between NPs with specific amino acids.

METHODS

Retrieval of chemokine and other cytological proteins three-dimensional (3D) conformation

The coordinates of selected proteins (Table 1) were obtained from the RCSB protein data bank (http://www.rcsb.org/pdb/home/)
The protein molecules were prepared for the molecular interaction studies using the prepare protein protocols of Biovia Discovery Studio 4.0 software suit. Prepared protein protocol fixed various protein structure errors such as missing atoms in incomplete residues, missing loop regions, alternate conformations (disorder), non-standard atom names, and incorrect protonation state of titratable residues. For molecular docking studies, we defined the active sites of proteins using in silico literature, [24] and rest of active site of proteins were retrieved using COACH server [25]. COACH is a meta-server for the prediction of protein-ligand binding site prediction. The prediction of the active site is mainly based on two comparative methods, TM-SITE and S-SITE, which recognize ligand-binding templates from the BioLiP protein function database [25] by binding-specific substructure and sequence profile comparisons. The assessment of the active site was done using the confidence score (C-score) that determined the accuracy of the active site prediction. C-score ranges 0–1, where a higher score indicates a more reliable prediction and this score is defined based on the quality of the threading alignments and the convergence of the I-TASSER's structural assembly refinement simulations.

\[
C \text{- score} = \ln \left[ \frac{M}{M_{\text{tot}}} \times \frac{1}{<\text{RMSD}>} \times \frac{1}{7} \sum_{i=1}^{7} Z(i) \right] 
\]

Where \( M \) is the number of structure decoys in the cluster and \( M_{\text{tot}} \) is the total number of decoys generated during the I-TASSER simulations, RMSD is the average deviation of the decoys from the cluster centroid. \( Z(i) \) is the Z-score of the best template generated by \( i \)-th threading in the seven LOMETS programs and \( Z(i) \) is a program-specified Z-score cutoff for distinguishing between good and bad templates. The active site residues of selected chemokine and other cytological proteins are shown in Fig. 1.

Investigate the consequence of the interaction of ZnO-NP on biological processes

After molecular docking study, it is important to understand the biological processes in which these proteins were plays important role. We can comprehensive understand and actual impact of the docking in the biological system. To understand the biological impact, we have retrieved all the biological functions of the proteins which were taken in the study in a form of network that interacts to accomplish a process to the level with in the cell or organism. Different biological functions of chemokines and other cytological proteins were accessed using PANTHER (http://pantherdb.org) (protein analysis through evolutionary relationships). Classification system was designed to classify proteins (and their genes) to facilitate high-throughput analysis.

RESULTS AND DISCUSSION

In this study, we have taken cellular proteins into consideration for the examination of their interactions with ZnO-NP and the possible functions that can affect the physiology. All the putative targets of ZnO-NP and the active site predictions were carried out using COACH meta-server. The best active sites prediction base on the C-score of COACH meta-server for IL-1B and CCL-18 proteins are 0.23 and 0.26. In our docking studies, we have defined the active site of proteins to perform control docking with ZnO-NP. The best docking poses of ZnO-NP with proteins based on AutoDock binding energy were analyzed further. The best docking energy of ZnO-NP with P-38 (~8.81 Kcal/Mol), a total of 4 hydrogen bonds with GLY202, GLU203, ILE204, VAL369 and 4 electrostatic bonds formed with ASP43, GLU203, ASP370, PHE371, and also 2 Metal Acceptor bonds with ASP365 and VAL369 amino acid residues which clearly indicate that the ZnO-NP strongly bind to the active site cavity. We observed the second best docking energy (~7.64 Kcal/Mol) of ZnO-NP with NF-kB protein, it forms 5 hydrogen bonds with ARG57, HIS67, GLY68, PRO71, and...
Asian J Pharm Clin Res, Vol 11, Issue 3, 2018, 441-446

Singh et al.

and SER243, 3 metal acceptor bonds with GLY55, ARG57, and HIS67 and 1 electrostatic bond with PHE56 amino acid residues, and it also has strong binding in the active site cavity. On the other side, we observed least binding affinity for ZnO-NP with CCL-18 (−3.13 Kcal/Mol), whereas it forms only 3 hydrogen bonds and 4 metal acceptors with GLY5, ASN7, and GLN34 amino acid residues. The binding energies of other proteins, namely, ICAM-1, IL8, MMP-9, IL-1B, and CD-35 proteins with ZnO-NP are listed in Table 1.

From the molecular docking interactions, we have extracted the key residues of proteins which play important role in the binding of ZnO-NP more efficiently GLY which is hydrophobic in nature and present in 1I1B, 3W8Q, 1H6J, and 1I1B proteins. The rest of key residues interacting with proteins are PHE, ARG, ASP, GLN, and ASN and their nature were given in Table 2.

The amino acids show least interaction with ZnO-NP is LYS, VAL, THR, TYR, TRP, and LEU. Details of molecular interactions of ZnO-NP with chemokines and other cytological proteins are provided in Supplementary Table 1 and the best interacting pose was shown in Fig. 1. The molecular docked proteins have a specific role in biological processes which can affect by the interaction with ZnO-NP. The outcome from this study clearly indicated that the ZnO-NP inhibits the process of response to a stimulus, cellular process, and biological adhesion more effectively and other processes were given in Fig. 2.

| Proteins | NP     | Energy in (Kcal/Mol) | Total number of H Bond | Metal acceptor | Electrostatic | Attractive charge |
|----------|--------|----------------------|------------------------|----------------|---------------|------------------|
| 1I1B (IL-1B) | ZnO-NP | −3.23                | 3                      | -              | -             | 3                |
| 1GKG (CD 35) |        | −3.92                | 2                      | 1              | -             | -                |
| 1L6j (MMP-9) |        | −7.27                | 5                      | 2              | 1             | 1                |
| 1L8 (IL8) |        | −5.14                | 2                      | 2              | -             | 1                |
| 4MHE (CCL-18) |        | −3.13                | 3                      | 4              | -             | -                |
| 1P53 (ICAM-1) |        | −4.95                | 2                      | 1              | -             | 2                |
| 1SVC (NF-kB) |        | −7.64                | 5                      | 3              | 1             | -                |
| 3W8Q (P-38) |        | −8.81                | 4                      | 2              | 1             | 3                |

Table 1: Docking energies and bond information of ZnO-NP with chemokines and other cytological proteins

Fig. 2: Illustration of the interaction network of zinc oxide nanoparticle (ZnO-NP) with chemokines and other cytological proteins. Nodes with different colors represent various Biological functions of proteins which were inhibited by ZnO-NP. The figure legend represents the function of these proteins

Protein ICAM-1 also known as CD54 (cluster of differentiation 54) has an important role in cell-cell signaling for stabilization of cell-cell interaction and facilitates the leukocyte endothelial transmigration [34,35]. The ICAM-1 plays a significant role in spermatogenesis due to its antagonistic effect on the tight junctions forming the blood testis barrier [34]. P-38 has an important function in cell-cell signaling against stress and is responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock. It is also involved in cell differentiation, apoptosis, and autophagy [36,37]. Similarly, NF-kB plays a very important role in several cellular functions. NF-kB controls the cellular responses as it belongs to the category of "rapid-acting" primary transcription factor, i.e., a transcription factor which was present in cells in an inactive state and does not undergo new protein synthesis to become activated [38,39]. Several innate and adaptive immune response genes are regulated by a transcription factor (NF-kB) [40-42]. Interaction of ZnO-NP with proteins might be altering the functional properties, as results may affect stabilization of cell-cell interactions. It is a newer approach to determine the ZnO-NP interaction with proteins using docking, without any surface modification of NP.
Zinc oxide nanoparticles induce migration and dosimetry. Environ

CONCLUSION

Using molecular docking as computational approaches could be adopted for the screening of all the NPs, which can bind to the target with experimental or modeled structures. A number of studies already reported that engineer NP particles (ENPs) interact with the biological macromolecules. Recent studies have shown that ENPs inhibit enzyme activity due to their interaction with the active site or binding directly with the substrate [43,44]. Using molecular docking studies, we conclude that the ZnO-NP is strongly interacting with the chemokines and other cytoplasmic proteins on its activation site and thus responsible for blocking of the activation stimulus for chemokines, and other cytoplasmic proteins to initiate the biological signals for the proper functioning of these proteins. In contrast, from the above results, it indicates the key interacting amino acid residues with ZnO-NP and their nature. Which plays important role in the interaction of ZnO-NP with proteins.

ACKNOWLEDGMENTS

We express our gratitude to Amity University Uttar Pradesh, Lucknow Campus, for providing the laboratory facilities and encouragement.

AUTHORS CONTRIBUTIONS

Mr. Krishna Pal Singh: Carried out the Research work. Dr. Qamar Rahman: Provided guidance, critical review and revision. Dr. Anupam Dhasmana: Helped while caring the experiments.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

REFERENCES

1. Amelia M, Lincheneau C, Silvi S, Credi A. Electrochemical properties of CdSe and CdTe quantum dots. Chem Soc Rev 2012;41:5728-43.
2. Yan L, Zheng YB, Zhao F, Li S, Gao X, Xu B, et al. Chemistry and physics of a single atomic layer: Strategies and challenges for functionalization of graphene and graphene-based materials. Chem Soc Rev 2012;41:97-114.
3. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science 2006;311:622-7.
4. Buza C, Pacheco II, Robbie K. Nanomaterials and nanoparticles: Sources and toxicity. Biointerphases 2007;2:MR17-71.
5. De Stefano D, Carnuccio R, Maiuri MC. Nanomaterials toxicity and cell death modalities. J Drug Deliv 2012;2012:167896.
6. Oberdörster G. Nanotoxicology: In vitro-in vivo dosimetry. Environ Health Perspect 2012;120:A13.
7. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 2005;113:823-39.
8. Fan Z, Lu JG. Zinc oxide nanostructures: Synthesis and properties. J Nanosci Nanotechnol 2005;5:1561-73.
9. Nations S, Wages M, Callas JE, Maal J, Theodorakis C, Cobb GP, et al. Acute effects of Fe2O3, TiO2, ZnO and CuO nanomaterials on Xenopus laevis. Chemosphere 2011;83:1053-61.
10. Jeng HA, Swanson J. Toxicity of metal oxide nanoparticles in mammalian cells. J Environ Sci Heal Part A 2006;41:2699-711.
11. Horie M, Nishio K, Fujita K, Endoh S, Miyauchi A, Saito Y, et al. Protein adsorption of ultrafine metal oxide and its influence on cytotoxicity toward cultured cells. Chem Res Toxicol 2009;22:543-53.
12. Wu W, Samet JM, Peden DB, Bromberg PA. Phosphorylation of p65 is required for zinc oxide nanoparticle–induced interleukin 8 EXPRESSION in human bronchial epithelial cells. Environ Health Perspect 2010;118:982-7.
13. Hackenberg S, Scherzer A, Techau A, Kessler M, Froelich K, Ginzkey C, et al. Cytotoxic, genotoxic and pro-inflammatory effects of zinc oxide nanoparticles in human nasal mucosa cells in vitro. Toxicol In Vitro 2011;25:657-63.
14. Babin K, Antoine F, Goncalves DM, Girard D. TiO2, ceO2 and ZnO nanoparticles and modulation of the degranulation process in human neutrophils. Toxicol Lett 2013;221:57-63.
15. Yuan L, Wang Y, Wang J, Xiao H, Liu X. Additive effect of zinc oxide nanoparticles isosorbin on apoptosis in human hepatoma cell line. Toxicol Appl Pharmacol 2014;278:16-25.
16. Suzuki Y, Tada-Oikawa S, Ichihara G, Yabata M, Izouka K, Suzuki M, et al. Zinc oxide nanoparticles induce migration and adhesion of monocytes to endothelial cells and accelerate foam cell formation. Toxicol Appl Pharmacol 2014;278:16-25.
17. Li CH, Liao PL, Shyu MK, Liu CW, Kao CC, Huang SH, et al. Zinc oxide nanoparticles-induced intercellular adhesion molecule 1 expression requires Rac1/Cdc42, mixed lineage kinase 3, and c-Jun N-terminal kinase activation in endothelial cells. Toxicol Sci 2012;134:262-72.
18. Sharma V, Anderson D, Dhowan A. Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2). Apoptosis 2012;17:852-70.
19. Song J, Du L, Feng Y, Wu W, Yan Z. Pyroptosis induced by zinc oxide nanoparticles in A549 cells. Wei Sheng Yan Jiu 2013;42:273-6.
20. Chuang KJ, Lee KY, Pan CH, Lai CH, Lin LY, Ho SC, et al. Effects of zinc oxide nanoparticles on human coronary artery endothelial cells. Food Chem Toxicol 2016;93:138-44.
21. Umrani RD, Paknikar KM. Zinc oxide nanoparticles show antidiabetic activity in streptozotocin-induced type 1 and 2 diabetic rats. Nanomedicine (Lond) 2014;9:89-104.

22. Pandurangan M, Veerappan M, Kim DH. Cytotoxicity of zinc oxide nanoparticles on antioxidant enzyme activities and mRNA expression in the cocultured C2C12 and 3T3-L1 cells. Appl Biochem Biotechnol 2015;175:1270-80.

23. Kumar A, Dhawan A, Shanker R. The need for novel approaches in ecotoxicity of engineered nanomaterials. J Biomed Nanotechnol 2011;7:79-89.

24. Ranjan S, Dasgupta N, Chinnappan S, Ramalingam C, Kumar A. A novel approach to evaluate titanium dioxide nanoparticle–protein interaction through docking: An insight into mechanism of action. Proc Natl Acad Sci India Sect B Biol Sci 2015;87:937-43.

25. Yang J, Roy A, Zhang Y. BioLiP: A semi-manually curated database for biologically relevant ligand-protein interactions. Nucleic Acids Res 2013;41:D1096-103.

26. Rahman S, Farooqui SA, Rai A, Kumar R, Santra C, Prabhakaran VC, et al. Mesoporous TUD-1 supported indium oxide nanoparticles for epoxidation of styrene using molecular O2. RSC Adv 2015;5:46850-60.

27. Sahare P, Moon A. In silico modelling of β-lactam resistant enterococcus faecalis pbp4 and its interactions with various phyto-ligands. Int J Pharm Pharm Sci 2016;8:151-5.

28. Dharani R, Ranjitha R, Sripathi R, Ali Muhammad KS, Ravi S. Docking studies in target proteins involved in antibacterial action mechanisms: Alkaloids isolated from Sceutella genus. Asian J Pharm Clin Res 2016;9:121-5.

29. Morris GM, Goodsell DS, Olson AJ. Automated docking of flexible ligands: Parallel applications of autoDock 2.4. J Comput Aided Mol Des 1996;10:293-304.

30. Benyamini H, Shulman-Peleg A, Wolfson HJ, Belgorodsky B, Fadeev L, Gozin M. Interaction of C60-fullerene and carboxyfullerene with proteins: Docking and binding site alignment. Bioconjug Chem 2006;17:378-86.

31. Baweja L, Gurbani D, Shanker R, Pandey AK, Subramanian V, Dhawan A, et al. C60-fullerene binds with the ATP binding domain of human DNA topoisomerase II alpha. J Biomed Nanotechnol 2011;7:177-8.

32. Patel A, Smita S, Rahman Q, Gupta SK, Verma MK. Single wall carbon nanotubes block ion passage in mechano-sensitive ion channels by interacting with extracellular domain. J Biomed Nanotechnol 2011;7:183-5.

33. Pandurangan M, Veerappan M, Kim DH. Cytotoxicity of zinc oxide nanoparticles on antioxidant enzyme activities and mRNA expression in the cocultured C2C12 and 3T3-L1 cells. Appl Biochem Biotechnol 2015;175:1270-80.

34. Xiao X, Mruk DD, Cheng CY. Intracellular adherence molecules (ICAMs) and spermatogenesis. Hum Reprod Update 2013;19:167-86.

35. Bai R, Yi S, Zhang X, Liu H, Fang X. Role of ICAM-1 polymorphisms (G241R, K469E) in mediating its single-molecule binding ability: Atomic force microscopy measurements on living cells. Biochem Biophys Res Commun 2014;448:372-8.

36. Kao YT, Hsu WC, Hu HT, Hsu SH, Lin CS, Chiu CC, et al. Involvement of p38 mitogen-activated protein kinase in acquired gemcitabine-resistant human urothelial carcinoma sublines. Kaohsiung J Med Sci 2014;30:323-30.

37. Javadov S, Jang S, Agostini B. Crosstalk between mitogen-activated protein kinases and mitochondria in cardiac diseases: Therapeutic perspectives. Pharmacol Ther 2014;144:202-25.

38. Pavlová S, Klucska K, Vašíček D, Ryban L, Harrath AH, Alwaseil SH, et al. The involvement of SIRT1 and transcription factor NF-κB (p50/p65) in regulation of porcine ovarian cell function. Anim Reprod Sci 2013;140:180-8.

39. Marinho HS, Real C, Cynne L, Soares H, Antunes F. Hydrogen peroxide sensing, signaling and regulation of transcription factors. Redox Biol 2014;2:535-62.

40. Colvin VL. The potential environmental impact of engineered nanomaterials. Nat Biotechnol 2003;21:1166-70.

41. Hayden MS, West AP, Ghosh S. NF-κB and the immune response. Oncogene 2006;25:6758-6780.

42. Jin J, Hu H, Li HS, Yu J, Xiao Y, Brittain GC, et al. Noncanonical NF-κB pathway controls the production of Type I interferons in antiviral innate immunity. Immunity 2014;40:342-54.

43. Kain J, Karlsson HL, Möller L. DNA damage induced by micro- and nanoparticles – interaction with FPG influences the detection of DNA oxidation in the comet assay. Mutagenesis 2012;27:491-500.

44. Magdolenova Z, Collins A, Kumar A, Dhawan A, Stone V, Dusinska M, et al. Mechanisms of genotoxicity. A review of in vitro and in vivo studies with engineered nanoparticles. Nanotoxicology 2014;8:233-78.
| Residues | Distance | Category | Type |
|----------|----------|----------|------|
| Zn0: ZnP-38:GLU203:OE2 | 4.06365 | Electrostatic | Attractive charge |
| Zn0: ZnP-38:ASP370:OD1 | 5.59144 | Electrostatic | Attractive charge |
| Zn0: 0-P-38:VAL369:HN | 2.10758 | Hydrogen bond | Conventional hydrogen bond |
| Zn0: 0-P-38:GLY202:O | 3.32089 | Hydrogen bond | Conventional hydrogen bond |
| Zn0: 0-P-38:GLY203:CA | 2.88581 | Hydrogen bond | Carbon-hydrogen bond |
| Zn0: ZnP-38:ASP43:OD1 | 2.9422 | Attractive charge | Metal acceptor |
| Zn0: ZnP-38:ASP365:O | 2.9422 | Attractive charge | Metal acceptor |
| Zn0: ZnP-38:ASP370:OD1 | 5.59144 | Electrostatic | Attractive charge |
| Zn0: ZnP-38:ASP38:OD1 | 3.3466 | Hydrogen bond | Conventional hydrogen bond |
| Zn0: ZnP-38:ASP43:OD1 | 2.9422 | Attractive charge | Metal acceptor |
| Zn0: ZnP-38:ASP365:O | 2.9422 | Attractive charge | Metal acceptor |
| Zn0: ZnP-38:ASP370:OD1 | 5.59144 | Electrostatic | Attractive charge |
| Zn0: ZnP-38:ASP38:OD1 | 3.3466 | Hydrogen bond | Conventional hydrogen bond |
| Zn0: ZnP-38:ASP365:O | 2.9422 | Attractive charge | Metal acceptor |
| Zn0: ZnP-38:ASP370:OD1 | 5.59144 | Electrostatic | Attractive charge |
| Zn0: ZnP-38:ASP38:OD1 | 3.3466 | Hydrogen bond | Conventional hydrogen bond |
| Zn0: ZnP-38:ASP365:O | 2.9422 | Attractive charge | Metal acceptor |