BioNanoScience 2017 vol.7 N1, pages 229-232

Computational Exploration of Reactivity of 6-Methyluracil/Imidazole-2-Carbaldehyde Oxime Conjugate

Lushchekina S., Ayupov R., Semenov V., Petrov K., Masson P.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2016, Springer Science+Business Media New York.Molecular docking and ab intio quantum mechanical calculations were used to assess the nucleophilic reactivity of conjugates of 6-methyluracil and imidazole-2-carbaldehyde oxime. Minimum energy profiles for oxime group rotation and proton transfer were calculated for isolated conjugate. Results indicated that proton transfer and activation are possible. Results suggests that the compound can be active itself, reacting with esters in a way, similar to enzymatic histidine-containing catalytic triad. Thus, this compound is of potential interest for direct scavenging organophosphorus inhibitors of cholinesterases and/or as co-reagent in cholinesterase-based pseudocatalytic bioscavengers.

http://dx.doi.org/10.1007/s12668-016-0347-1

Keywords

Acetylcholinesterase, Oxime, Quantum chemistry, Reactivation

References

[1] Sit, R. K., Fokin, V. V., Amitai, G., Sharpless, K. B., Taylor, P., Radić, Z. (2014). Imidazole aldoximes effective in assisting butyrylcholinesterase catalysis of organophosphate detoxification. Journal of Medicinal Chemistry, 57(4), 1378–1389. doi:10.1021/jm401650z.

[2] De la Manche, I. S., Verge, D. E., Bouchaud, C., Coq, H., Sentenac-Roumanou, H. (1979). Penetration of oximes across the blood–brain barrier. A histochemical study of the cerebral cholinesterases reactivation. Experientia, 35(4), 531–532.

[3] Kiffer, D., & Minard, P. (1986). Reactivation by imidazo-pyridinium oximes of acetylcholinesterase inhibited by organophosphates. Biochemical Pharmacology, 35(15), 2527–2533. doi:10.1016/0006-2952(86)90050-x.

[4] Legler, P. M., Soojhawon, I., Millard, C. B. (2015). A conformational change in the peripheral anionic site of Torpedo californica acetylcholinesterase induced by a bis-imidazolium oxime. Acta Crystallographica Section D: Biological Crystallography, 71(Pt 9), 1788–1798. doi:10.1107/S1399004715011281.

[5] Masson, P. (2016). Novel approaches in prophylaxis and treatment of organophosphorus poisoning. Phosphorus, sulfur, and silicon and the related elements, in press. doi:10.1080/10426507.2016.1211652

[6] Renou, J., Dias, J., Mercey, G., Verdelet, T., Rousseau, C., Gastellier, A.-J., et al. (2016). Synthesis and in vitro evaluation of donepezil-based reactivators and analogues for nerve agent-inhibited human acetylcholinesterase. RSC Advances, 6(22), 17929–17940. doi:10.1039/c5ra25477a.

[7] Kharlamova, A. D., Lushchekina, S. V., Petrov, K. A., Kots, E. D., Nachon, F. V., Villard-Wandhammer, M., et al. (2016). Slow-binding inhibition of acetylcholinesterase by an alkylammonium derivative of 6-methyluracil: mechanism and possible advantages for myasthenia gravis treatment. The Biochemical Journal, 473(9), 1225–1236. doi:10.1042/BCJ20160084.

[8] Amitai, G., Gez, R., Raveh, L., Bar-Ner, N., Grauer, E., Chapman, S. (2016). Novel bifunctional hybrid small molecule scavengers for mitigating nerve agents toxicity. Chemico-Biological Interactions. doi:10.1016/j.cbi.2016.04.036.

[9] Nemukhin, A. V., Grigorenko, B. L., Lushchekina, S. V., Varfolomeev, S. D. (2012). Quantum chemical modelling in the research of molecular mechanisms of enzymatic catalysis. Russian Chemical Reviews, 81(11), 1011–1025. doi:10.1070/RC2012v081n11ABEH004311.

[10] Semenov, V. E., Zueva, I. V., Mukhamedyarov, M. A., Lushchekina, S. V., Kharlamova, A. D., Petukhova, E. O., et al. (2015). 6-methyluracil derivatives as bifunctional acetylcholinesterase inhibitors for the treatment of Alzheimer's disease. ChemMedChem, 10(11), 1863–1874. doi:10.1002/cmdc.201500334.

[11] Fukui, K., Yonezawa, T., Shingu, H. (1952). A molecular orbital theory of reactivity in aromatic hydrocarbons. The Journal of Chemical Physics, 20(4), 722. doi:10.1063/1.1700523.