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The biological activity and molecular docking studies of three multiple myeloma drugs

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In this work, we have compared the biological activity of lenalidomide and pomalidomide, which are analogues of thalidomide, a multiple myeloma drug by calculating Lipophilicity (Log P), aqueous solubility (Log S) and molecular weight (MW) and found that pomalidomide is biologically more active than lenalidomide. Furthermore, we have studied the molecular docking of above three drug molecules with human activated C-protein, which is responsible for multiple myeloma and noticed that pomalidomide binds more efficiently than lenalidomide. Moreover, the binding patterns of three drugs are slightly different implying their mechanism of action.

Introduction

C-reactive protein (CRP) is an annular (ring-shaped) pentameric protein found in the blood plasma, the levels of which rise in response to inflammation (i.e., C-reactive protein is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion from macrophages and T-cells). It is the member of a small pentraxins family. In monomer form, it consists of 224 amino acids [1] and an annular pentameric discoid shape. CRP binds to the phosphocholine expressed on the surface of dead or dying cells and some bacteria [2]. This activates the complement system, promoting phagocytises by macrophages, which clears necrotic, and apoptotic cells and bacteria. Multiple myeloma is a cancer of the blood which is associated with the accumulation of a plasma cell clone in the bone marrow [1]. During the 6^{th}-7^{th} decades of 20^{th} century, thalidomide was used to treat this disease. The teratogenic properties of thalidomide have been employed for the development of new drug namely, lenalidomide [3]. Another derivative of thalidomide, pomalidomide, which is originally discovered to inhibit angiogenesis in the last decade of 20^{th} century [4] has also been used for the same treatment.

In this paper, we evaluate and compare the biological activity of lenalidomide and pomalidomide by calculation of log *P* and log *S*. These two parameters are deciding factors for biological response or toxicity of molecules. Furthermore, we have performed their docking studies into human activated C-protein in order to reveal binding pattern and affinity of these molecules.

Methodology

The equilibrium structures at B3LYP/6-311++G(d,p) level using Gaussian 09 program [5] of molecules have been used. The schematic structures of thalidomide as well as its derivatives lenalidomide and pomalidomide are shown in Fig. 1. Lenalidomide and pomalidomide are derivative compounds of thalidomide which is composed of two amide moieties, the phthalimide ring and glutarimide ring. In pomalidomide, one additional CH_2 group attached to phthalimide ring. The calculation of Log P, Log S and molecular weight (MW) parameters has been performed by ALOGPS 2.1 program [6]. The molecular docking studies are performed by Hex 8.0 program. The target protein is collected from protein data bank (PDB ID: 1AUT) [7].

Results and discussion

Biological activity

The calculated Log P, Log S and MW values are listed in Table 1. The MW of pomalidomide is higher than that of lenalidomide. The lipophilicity (Log P) and aqueous solubility (Log S) are well recognized for its importance in Quantitative Structure Property Relationship (QSPR) studies. Log P is closely related to transport property of drugs and their interaction with receptors while log S is an important factor affecting its bioavailability. The calculated value of log P for lenalidomide is -0.43 while that for pomalidomide is 0.02. The pomalidomide works in multiple ways to slow or kill myeloma cells due to high value of log P. It directly affects the tumor cells .

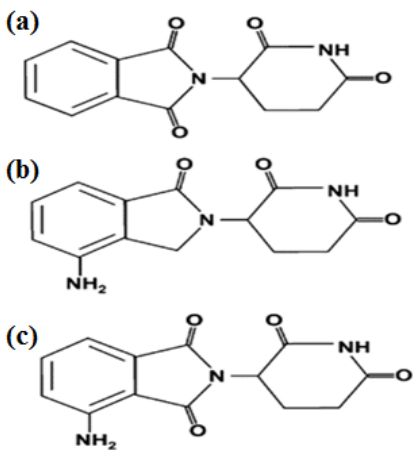

Fig. 1. Schematic structures of thalidomide (a), lenalidomide (b) and pomalidomide (c).

The increased log P value further suggests that it is comparatively easier for pomalidomide to diffuse across the cell membranes however organic (lipid) solubility may not be very high. In practice, about 85% of drugs have log S values in the range of -1 to -5 and virtually none have values below -6 [8, 9]. Values above -1 are not problematic, though they are often associated with highly polar molecules that may have low membrane permeability in the absence of active transport. Thus these parameters also indicate towards more biologically active nature of pomalidomide.

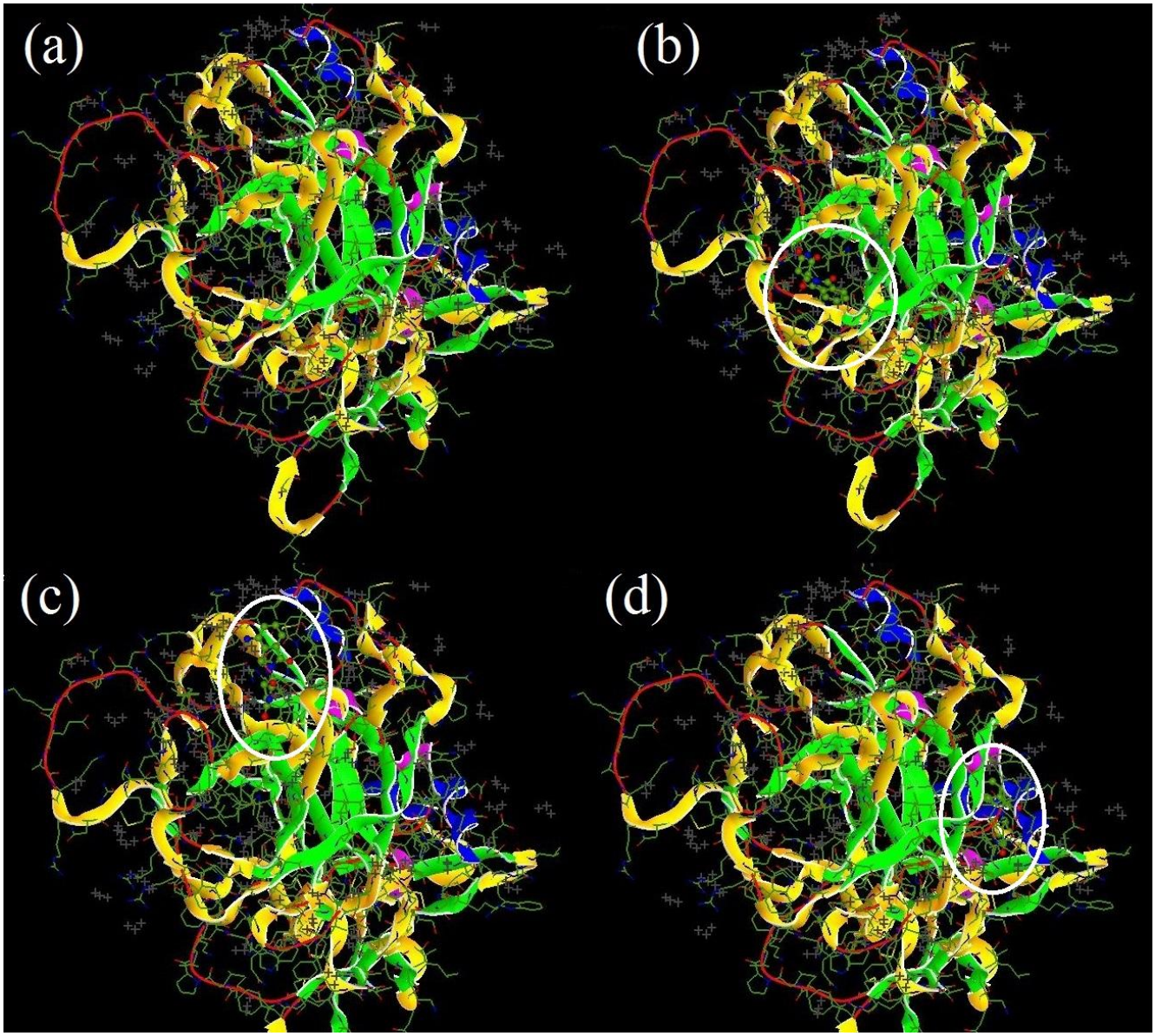

Fig. 2. Representative structure of human activated C-protein (a), docked with thalidomide (b), lenalidomide (c) and pomalidomide (d). The docking region is encircled by white color.

Table 1. Molecular weight (MW), Lipophilicity (Log P) and Aqueous Solubility (Log S)

Parameters	Lenalidomide	Pomalidomide
MW	259.29	273.27
Log P	-0.43	0.02
Log S	-2.05	-2.03

Table 2. Docking scores for three multiple myeloma drugs

Ligand	E-value
Thalidomide	-115.85
Lenalidomide	-109.69
Pomalidomide	-111.33

Conclusions

We have studied thalidomide, a multiple myeloma drug molecule and its two analogues viz. lenalidomide and pomalidomide. We have calculated some biological activity parameters and established that pomalidomide should be more active as compared to lenalidomide. This is further supported by our molecular docking studies which showed that three molecules bind to the same protein receptor in different ways. This may allow us to conclude that although three molecules act against multiple myeloma disease, their biological mechanisms of action may be slightly different.

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Notes and References

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1. Available online at http://www.ncbi.nlm.nih.gov/protein/30224
2. D. Thompson, M. B. Pepys and S. P. Wood *Structure* **7** (1999) 169.
3. X. Armoiry, G. Aulagner and T. Facon, *Journal of Clinical Pharmacy and Therapeutics* **33** (2008) 219.
4. Pomalyst (Pomalidomide) Approved By FDA For Relapsed And Refractory Multiple Myeloma, The Myeloma Beacon News (Retrieved 2013-08-10)
5. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski and D.J. Fox, Gaussian 09, Revision B.01, Gaussian Inc., Wallingford, CT (2010).
6. Available online at http://www.vcclab.org/lab/alogps/start.html
7. Available online at http://www.rcsb.org/pdb/explore.do?structureId=1aut
8. J. Huuskonen, M. Salo and J. Taskinen, *Journal of Chemical Information and Computational Science* **38** (1998) 450.
9. W. L. Jorgensen and E. M. Duffy, *Bioorganic and Medicinal Chemistry Letters* **10** (2000) 1155.
10. V. Srivastava, A. Kumar, B. N. Mishra and M. I. Siddiqui, *Bioinformation* 4 (2008) 180.