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Docking Studies of a Series of Fluphenazine as Potential 1RE1(X-Ray Crystal Structure of Caspase-3) Inhibitors: A Rational Approach to Anticancer Drug Design

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ABSTRACT

Phenothiazine (Pht) derivatives are an active compounds which have activity in inhibiting the caspase-3 enzyme in vitro. Docking simulation was done to determine and visualize the interaction of the 9 compounds with the caspase-3 enzyme. The results of docking simulations showed that four compounds can interact spontaneously with the caspase-3 enzyme. On the caspase-3 enzyme, interact most easily through the formation of hydrogen bonds with Arg286. On the ID10a compound interact most easily through the formation of two hydrogen bonds with Ser219 and Arg269. With the inhibitory effect on the enzyme caspase-3means preventing the cancer, indicating that the four compounds studied can be applied as anti-cancer agents.

1. Introduction

Phenothiazine (Pht) derivatives have a long history, with successive periods of interest in different areas of applied chemistry, such as: dyes, probes, pharmaceuticals, and electrochemistry [1]. Phenothiazine derivatives (Pht), among them also fluphenazine (FPh), apply an anti-psychotic activity by binding and inhibition of an variety of presynaptic dopaminergic receptors as well as for years various drugs from phenothiazine family have been used in psych-pharmacotherapy [2]. Besides their neuroleptic activity Pht also own cancer chemo-preventive activity, they inhibit the calmodulin, the protein kinase C, and decrease the transporter function of p-glycoprotein [3].

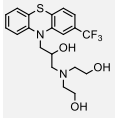
Importantly, recent papers documented an anti-cancer activity of various Pht in cultures of human being cancer cell lines [4, 5]. Randomized possible studies of patients with schizophrenia, treated with Pht found that the occurrence rate of cancer was smaller than in healthy people from the control group [6]. The mechanism of cancer prevention by Pht is weakly known. On the other hand, some experimental results revealed that various Pht compounds are able to cause in vitro a developed cell death (apoptosis) in tumor cells and/or in geno-toxically damaged cells [7, 8]. It is generally accepted that stimulation of apoptosis in cancer cells happens to be an important mechanism of action of cancer chemo-preventive drugs, and it is reasonable that a pro-apoptotic activity should prevail against a cytotoxic activity in the activity profile wanted for those drugs [9, 10]. Pht have been used for years in the treatment of patients with schizophrenia, and lately they are also assayed for anti-mutagenic and anti-cancer activities [11]. It was estimated that Pht showed strong pro-apoptotic activity in vitro [12, 13]. Nevertheless, their usefulness in cancer remedy in humans is limited by the serious negative effects on the central nervous system, mainly the extrapyramidal symptoms and introduction of the iatrogenic Parkinsonism [14]. Docking studies were performed to explore receptor-based conformation or binding pocket for each compound models. The primary screening of structure based drug design may be helpful to develop an effective anti-cancer drugs.

2. Experimental Methods

2.1 Molecular Docking

Nine molecules belonging to fluphenazine derivatives as anti-cancer inhibitors were taken from the literature and used for molecular docking analysis [15, 16]. Docking studies were employed to locate the appropriate binding orientations and conformations of these fluphenazine derivatives interacting with caspase-3 using the docking program PyRx. PyRx is a fast, flexible docking method that uses an incremental construction algorithm to place ligands into an active site. By default, the docking program produces 9 docked structures for each fluphenazine derivative. The conformation with the lowest docking energy in the most populated cluster is selected as the possible 'active' conformation against the 1RE1 active site. In the present study, 9 compounds were successfully docked into the 1RE1 site. The X-ray crystal structure of caspase-3 taken from the Protein Data Bank (PDB: 1RE1) was used to dock. At the beginning of docking, all the water molecules were removed, hydrogen atoms added and charges to the protein were applied. It is critical to search for the binding pocket of the prepared protein in docking studies. In PyRx (autodockvina) docking, the binding pockets can be defined either from a co-crystallized ligand or from a list of residues known to be part of the interacting site (or predicted de novo). The docking poses were ranked by PyRx (autodockvina) docking and the top 9 poses were selected. The ligands were then docked inside a cubic GRID box of the entire protein. Nine docking runs were performed for each compound in the dataset. In most cases the chosen pose was the top ranked solution.

Table 1 Results of Caspase-3 Enzyme Preparation(PDB code: 1RE1) and Phenothiazine (Pht) derivatives

Structures	Hydrogen bond (Å)	Hydrophobic Interaction	Binding energy (Kcal/mol)	pED_{50}
ID3a 	Thr246 (3.05), Asp205 (2.70), (2.87), Glu210 (3.10), (2.83).	His174, Glu209, Glu210, Thr207, Asn247.	-4.5	5.13

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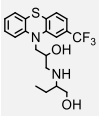
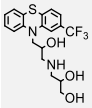
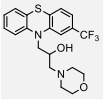
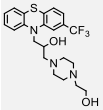
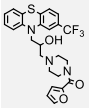
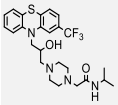
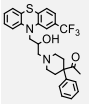
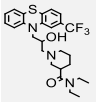
ID4a 	Lys278 (2.92), Lys276 (2.81).	Gly275, Tyr153, Leu279, Pro277	-5.9	5.22
ID5a 	Lys276 (2.92), Lys278 (3.11), Gly275 (3.30), Ty153 (3.21).	Pro277, Leu279	-5.6	4.84
ID6a 	Gly267 (2.88).	Leu279, Lys278, Phe280, Pro277, Tyr153	-6.0	5.17
ID7a 	Nil	Pro161, Lys197, Tyr198, Val200, Glu199, Glu162	-5.8	5.13
ID8a 	Arg286 (2.98)	Arg266, Phe265, Phe280, Lys278, Leu258, Ile282, Thr262	-6.5	5.09
ID9a 	Lys278 (3.16)	Ile282, Arg286, Phe280, Leu258, Thr262	-6.0	5.13
ID10a 	Ser219 (3.17), Arg269 (3.30)	Arg271, Lys220, Asn263, Lys260, Phe264	-6.6	4.71
ID11a 	Nil	Glu199, Tyr198, Arg194, Met162A, Lys197, Glu162, Pro161, Val200	-5.9	4.99

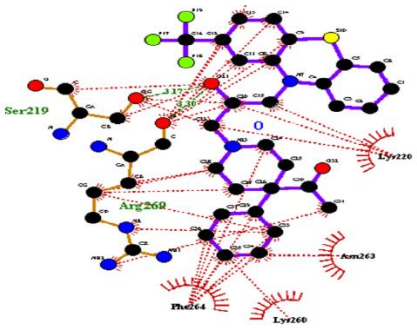


Fig. 1: Active enclave (ID10a) the enzyme caspase-3 and fluphenazine using LigPlot+

Fig. 1 Active Enclave (ID10a) the enzyme caspase-3 and fluphenazine using LigPlot*

3. Results and Discussion

A docking study could offer understanding the protein–ligand interactions and the structural features of the active site of the protein. All fluphenazine derivatives were docked into the binding site of caspase-3 and the energy scores of the ligands are also shown in Table 1, where precise correlations could be found between docking scores and pED_{50} values. A complete overview of PyRx (autodockvina) docking is presented in Fig. 1. Docking studies showed that ligand ID10a is suitably situated at the binding site and there are various interactions between it and the binding region of the enzyme. The fluphenazine substituent binds to the Caspase hinge region through two key hydrogen bond interactions: (1) between the O of Ser219 and the OH of the fluphenazine substituent (2) between the O of Arg269 and the OH of the fluphenazine substituent. The hydrogen bonding distances observed were 3.17 Å (O_ _ _ OH– Ser219) and 3.30 Å (O_ _ _ C=O–Arg269). Table 1 shows the docking mode of the least active fluphenazine derivative compound ID3a at the docking pocket. Similar to compound ID6a, compound ID9a was also docked at the same binding pockets having Phe280 amino acid residues. Results show that the O atom of the fluphenazine substituent forms a conservative hydrogen bond with (ID8a) Arg286 residue having 2.98 Å bond distance. O atom of the substituent of the fluphenazine also forms hydrogen bonding with (ID6a) HNH of Gly238 (O_ _ _ HNH-Gly267) with 2.88 Å bond length and (ID9a) C=O of Gly238 (O_ _ _C=O Lys278) with 3.16 Å bond length. The docking results reported in Table 1, reveal that hydrogen bonding may be responsible for activity, which may be further increased on adding high electronegative substitutions.

4. Conclusion

Docking results clearly reveal that the presence of an additional electronegative group at substitution (ID10a) forms more hydrogen bonds with their surrounding amino acid residues (2 hydrogen bonds with Ser219 and Arg269) and therefore possesses improved biological activity in comparison to compounds that possess less number of electronegative substitutions (ID7a and ID11a) at the aforementioned positions. The results obtained from moleculardocking studies can be served as a useful guideline for furthermodification of fluphenazine derivatives, which function as anti-cancer inhibitors.

Reference

[1] A. Srivastava, S. Jain, A.K. Nagawat, Electronic properties of nitrogen doped armchair single wall nanotubes: Ab-initio study, Quantum Mat. 2(6) (2013) 469-473.
[2] K.L. Claxton, J.J. Chen, D.M. Swope, Drug-induced movement disorders, J. Pharm. Pract. 20(6) (2007) 415-429.
[3] A. Jaszczyszyn, K. Gąsiorowski, P. Świątek, W. Malinka, K. Cieślik-Boczula, et al, Chemical structure of phenothiazines and their biological activity, Pharmacol. Rep. 64(1) (2012)16-23.
[4] H.H. Aung, C.Z. Wang, M. Ni, A. Fishbein, S.R. Mehendale, et al, Crocin from Crocus sativus possesses significant anti-proliferation effects on human colorectal cancer cells, Exp. Oncol. 29(3) (2007) 175-180.
[5] A. Bisi, M. Meli, S. Gobbi, A. Rampa, M. Tolomeoand, et al, Multidrug resistance reverting activity and antitumor profile of new phenothiazine derivatives, Bioorg. Med. Chem. 16(13) (2008) 6474-6482.
[6] V.S. Catts, S.V. Catts, B.I. O'toole, A.D.J. Frost, Cancer incidence in patients with schizophrenia and their first-degree relatives–a meta-analysis, Acta Psychiatr. Scand. 117(5) (2008) 323-336.
[7] M. Taler, I. Gil-Ad, L. Lomnitski, I. Korov, E. Baharav, et al, Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression, Eur. Neuropsychoph. 17(12) (2007) 774-780.
[8] J.H. Choi, Y.R. Yang, S.K. Lee, S.H. Kim, Y.H. Kim, et al, Potential inhibition of PDK1/Akt signaling by phenothiazines suppresses cancer cell proliferation and survival, Ann. NY Acad. Sci. 1138(1) (2008) 393-403.
[9] S.Y. Sun, N. Hailand, R. Lotan, Apoptosis as a novel target for cancer chemoprevention, J. Natl. Cancer Inst. 96(9) (2004) 662-672.
[10] M.J. Hoffmann, M. Müller, A.R. Florl, W.A. Schulz, The presumptive cancer-testis antigen CTCFL is regulated by DNA methylation, Onkologie. 28(2) (2005) 1-68.
[11] W. Malinka, Synthesis, pro-apoptotic activity and 2D-QSAR studies of new analogues of fluphenazine, Actapoloniae Pharmaceut. 71(1) (2014) 49-58.
[12] A. Jaszczyszyn, K. Gąsiorowski, P. Świątek, The chemosensitive activity of new fluphenazine analogues in human lymphocyte cultures after acid sphingomyelinase blockade, Book of programme and abstracts,25th Congress of the Polish Physiological Society, Olsztyn, Poland, 2011.
[13] S. Thomas, N. Sharma, E.B. Golden, H. Cho, P. Agarwal, et al, Preferential killing of triple-negative breast cancer cells in vitro and in vivo when pharmacological aggravators of endoplasmic reticulum stress are combined with autophagy inhibitors, Cancer Lett. 325(1) (2012) 63-71.
[14] D.F. Levinson, G.M. Simpson, E.S. Lo, T.B. Cooper, H. Singh, et al, Fluphenazme plasma levels, dosage, efficacy, and side effects, Am. J. Psychiatry 1 (1995) 765-771.
[15] F. Broccatelli, E. Carosati, A. Neri, M. Frosini, L. Goracci, et al, A novel approach for predicting P-glycoprotein (ABCB1) inhibition using molecular interaction fields, J. Med. Chem. 54(6) (2011) 1740-1751.
[16] D.L. Ma, D.S.H. Chan, C.H. Leung, Drug repositioning by structure-based virtual screening, Chem. Soc. Rev. 42(5) (2013) 2130-2141.

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