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In-Silico Study of Novel Folate Analogues as Anticancer which Inhibits Dihydrofolate Reductase

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Abstract

Dihydrofolate reductase (DHFR) has an important function in folic analogues biosynthesis which is used as nutrition for cells. In a specific cancer cell, DHFR has bigger expression than normal cells therefore it is good candidates as target to cancer chemotherap. In this research the screening have been done to 10-N-(4'-bromobenzoyl) folic acid and 10-N-(p-toluoyl) folic acid by in silico method. The result of molecular docking shows that those two compounds have more stable interaction than other DHFR inhibitors (methotrexate) but those two compound do not follow the Lipinsky's rule of 5 which is affected to its bioavailability.

Keywords: Cancer, DHFR, In-silico, Folate analogues

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1. Introduction

Cancer is cell which has uncontrollable growth rate and spread to another part of the body [1]. About 28.8 million people in the world is diagnosed cancer and 7.6 million died because of cancer in 2008 [2].

There is several enzyme which can be used as target for cancer chemotherapy such as ribonucleotide (RNR), timidilat sintase (TS) and dihidrofolate reductase (DHFR). DHFR contribute in de novo synthesis of timidilic acid and purin nucleotide thus these two compounds then becomes guanosine triphospate (GTP) which is important for cell cycle [3]. When DHFR is inhibited, it could hinder DNA and RNA synthesis then could cause in cell death.

Methotrexate is commercially available drug that can be used as cancer treatment and belong to folate analogues that can inhibit DHFR but this compound has several adverse effect such as anemia megaloblastic and neurotoxic [4]. Thus, we need a safer treatment for patient with cancer.

In this research, we did an in silico study of 2 folate analogues; 10-N-(4'-bromobenzoyl) folic acid and 10-N-(p-toluoyl)folic acid; as potentially cancer therapy and comparving them with methotrexate. We also assessing the bioavailability of those compound so it could be used orally.

2. Method

2.1. Target identification

Docking target for this research is dihydrofolate reductase (e.c.1.5.1.3) complexed with methotrexate (Fig. 1 PDBID – 1DDS) and was downloaded from RSCB Protein Data Bank (http://www.rcsb.org/). 1DDS is chosen because it contains methotrexate, which is commercially available medicine against cancer, thus can be used as a comparator.2.1. Spacing

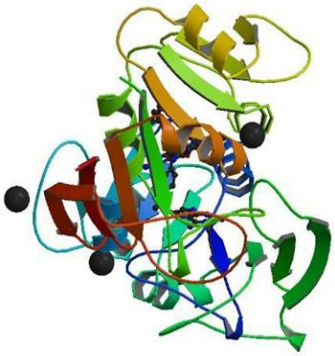

Fig. 1. Crystal structure of dihydrofolate reductase (e.c.1.5.1.3) complexed with methotrexate (PDBID – 1DDS)

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You must use single line spacing. However, when typing complicated mathematical text it is important to increase the space between the text lines in order to prevent sub- and superscript fonts overlapping one another and making your printed matter illegible. If you are using a desktop publishing program ensure that your auto adjust for interline spacing is suitably set to prevent overlapping but without leaving too much space.

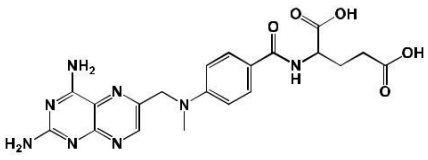
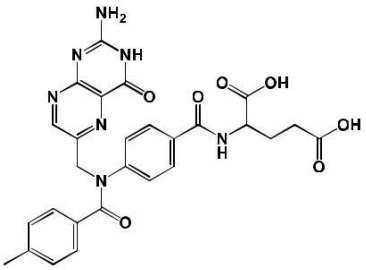
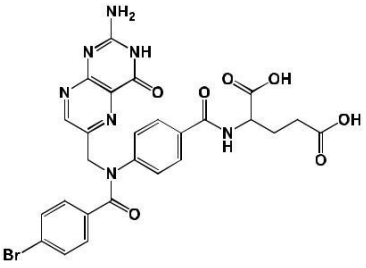
2.2. Molecule preparation and physicochemical analysis

We have created 2 folate analogues (Table 1) with ChemBioDraw Ultra 11.0 and their 3D structure was generated and energy minimized using ChemBio3D Ultra 11.0 (Table 2). Physicochemical properties of those compounds were calculated by Molinspiration Property Engine (v2014.11) internet tool.

2.3. Molecular docking

Molegro Virtual Docker 5.0.0 was used to generate docking results of the molecules with 1DDS. As for binding site identification, we used cavity 1 which have the largest volume. The docking parameter consists of max iterations 1500 and max population size 50. Pose generation with energy threshold 100.00, min: 10, quick: 10, max: 30 and for simplex evolution max steps 300, neighbour distance factor was set to 1.00.

Table 1
Physicochemical parameters of folate analogues

No	Molecular structure	Molecular parameters	
1		miLogP	-1.97
		TPSA	210.55
		atoms	33
		MW	454.45
		nON	13
		nOHNH	7
		violations	2
		nrotb	9
		volume	387.36
	Methotrexate		
2		miLogP	-0.64
		TPSA	221.57
		natoms	41
		MW	559.54
		nON	14
		nOHNH	6
		nviolations	3
		nrotb	10
		volume	474.59
	10-*N*-(p-toluoyl)folic acid		
3		miLogP	-0.28
		TPSA	221.57
		natoms	41
		MW	624.41
		nON	14
		nOHNH	6
		nviolations	3
		nrotb	10
		volume	475.92
	10-*N*-(4-bromobenzoyl)folic acid		

TPSA: topological surface area, MW: molecular weight, nON: hydrogen bond donors, nOHNH: hydrogen bond acceptors,

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Table 2
Interaction of folate analogues with 1DDS

No	Molecule	Energy minimized	Rerank score	∑ H Bonds	Interacting residues
1	Methotrexate	-15.70	-114.60	6	Ile94, Ile5, Tyr100, Arg 57, Asp27
2	10-*N*-(p-toluoyl)folic acid	29.14	-129.51	5	Leu54, Arg57, Pro53, Pro55
3	10-*N*-(4-bromobenzoyl)folic acid	25.53	-122,74	4	Leu54, Arg57, Pro53, Pro55

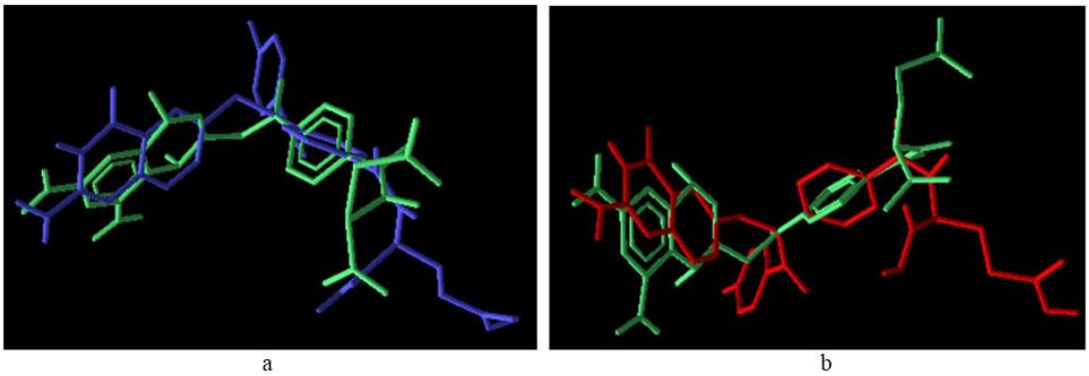

Fig. 2. (a) Configurational structure of 10-*N*-(4'-bromobenzoyl) folic acid (blue) and methotrexate (green). (b) Configurational structure of 10-*N*-(p-toluoyl) folic acid (red) and methotrexate (green)

3. Results and discussion

3.1. Physicochemical analysis

According to lipinski's rule of 5, orally active drugs need to have no more than one violation of this criteria so that drugs could have good oral bioavailability. This criteria states that a drug should have molecular weight < 500 Da; logP < 5; H Bond Donor < 5; and H bond acceptor < 10 [5]. From table 1, that 3 molecule including methotrexate has violated more than 1 of lipinski's rule.

This could be interpreted that those 3 molecules have bad bioavailability.

Methotrexate is belong to biopharmaceutical classification system (BCS) class III so it has good solubility but low permeability. The reason methotrexate could have good solubility is because it has glutamate side chain that consists of two carboxyl groups. Those 2 folate analogues would likely have similar properties because they have a similar structure as methotrexate.

3.2. Molecular docking

Docking simulation of those compounds with 1DDS was resulted in better interaction than methotrexate. This result can be seen because those two molecules have lower rerank score. A molecule which has lower rerank score would need less energy so that it could bind to the protein and make their complexed molecule-protein more stable than the other the molecule which has more rerank score.

According to table 2, compound 2 have the lowest rerank score but less hydrogen bond formed with protein and have mostly different ligand residues as methotrexate. This can be happened because even they both folate analogues, they have slightly different molecule configuration (Fig. 2) and causing different binding residues.

As for compound 3, it has 4-bromobrnzoyl substituted so it has more hydrophobicity than compound 2. This can be seen in table 1 that compound 3 have greater value in miLogP and molecular weight. But even so, compound 2 has lower rerank score than compound 3. Therefore, further investigation needs to be done in regard to finding the reason why this could happen

4. Conclusion

The result describes here to support that those 10-N-(4'-bromobenzyl)folic acid and 10-N-(p-toluoyl)folic acid potentially has anticancer properties and even greater than methotrexate. However, further studies are necessary to fully determine its potential as anticancer and its toxicity.

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Conflict and interest

The authors declare no conflict of interest.

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References

[1] D. Brundage, Oncologic Disorders at: J. T. DiPiro, et al. eds. Pharmacotherapy Principles dan Practice. New York: The McGraw-Hill Companies, Inc., 2008, p.1277.
[2] F. Bray, J.S. Ren, E. Masuyer, J. Ferlay, International Journal of Cancer, 132 (2013) 5.
[3] A. Gangjee, H.D. Jain, R.L. Kisliuk, Bioorganic and Medicinal Chemistry Letters, 15 (2005).
[4] S.C. Sweetman, Antineoplastic. In: S.C. Sweetman, ed. Martindale the Complete Drug Reference. 36th Edition ed. London: Pharmaceutical Press, 2009.
[5] T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson, J Chem Inf Comput Sci 41 (2001) 5.