Molecular *docking* study of iclaprim derivatives with potential antineoplastic activity

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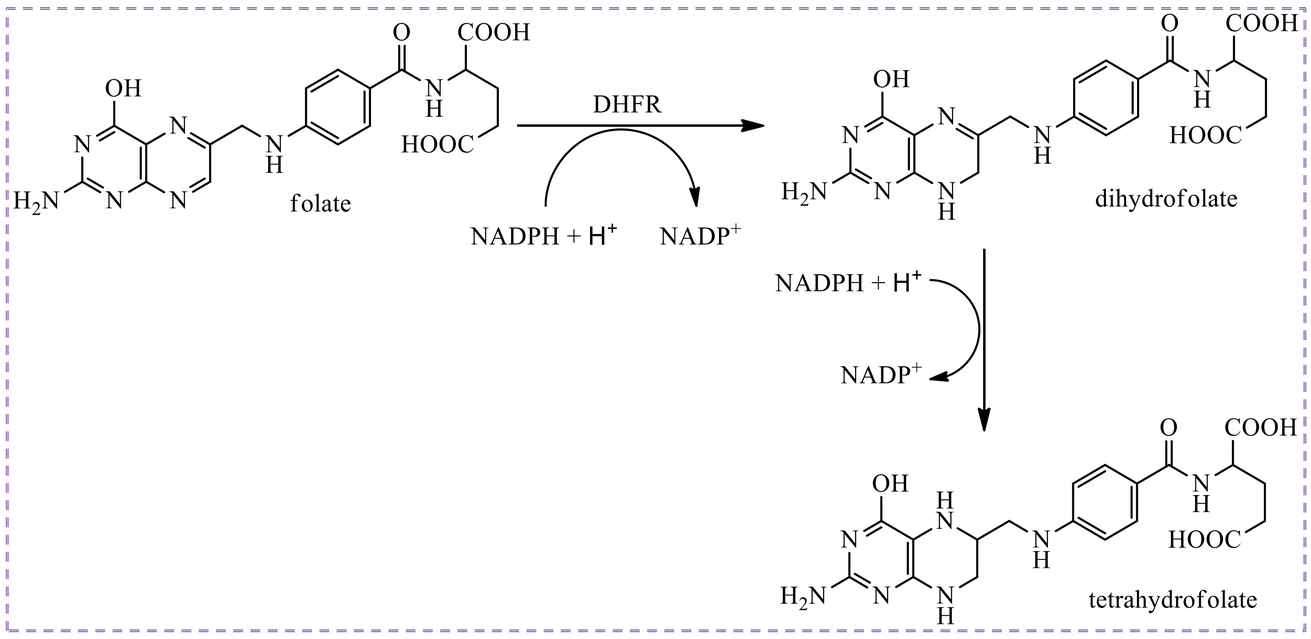
INTRODUCTION

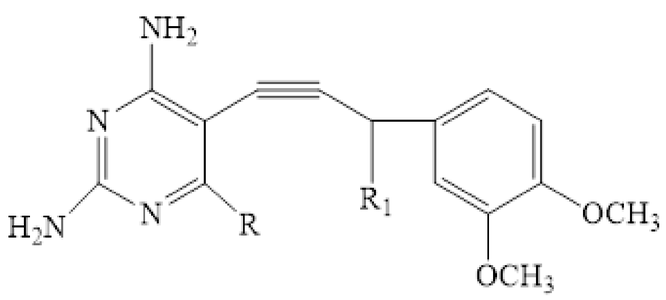
Dihydrofolate reductase (DHFR) is a member of the reductase enzyme family, which is ubiquitously expressed in all organisms. As an essential enzyme for cell growth and proliferation, DHFR is involved in purines and thymidylate synthesis and converts dihydrofolate to tetrahydrofolate (Scheme 1). DHFR has been a target for antiinflammatory and anticancer therapeutic agents which have been developed to target this key enzyme. Over the years, scientists have tried to improve existing therapy, so this has led to the discovery of iclaprim and propargyl-linked antifolates (PLA) whose characteristics can be used in the further design of DHFR inhibitors.



Scheme 1. Reactions catalyzed by DHFR

METHODS

This study aims to investigate the molecular docking of the 10 designed iclaprim derivatives into the human DHFR active site. The first series includes compounds containing substituted diaminopyrimidine and 2-cyclopropylin-7,8-dimethoxy-2*N*-chromene linked by a propargyl bridge (Table 1), while the second series contains compounds in which the substituted 2*N*-chromene is replaced by dimethoxybenzene (Table 2). All docking experiments were conducted using *AutoDock Vina*. The crystallographic structure of the human DHFR complex with a co-crystallized ligand (GHW), was taken from the Protein Data Bank database (PDB code: 3GHW).



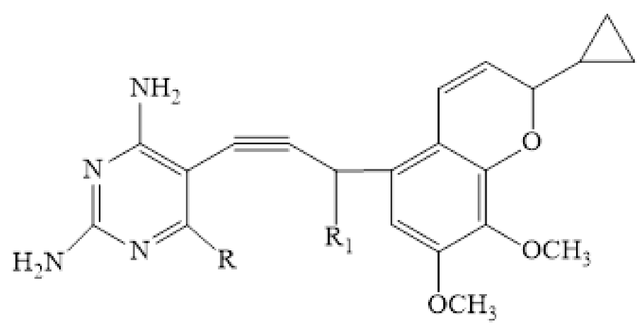


Table 1. The chemical structures of designed derivatives (1)

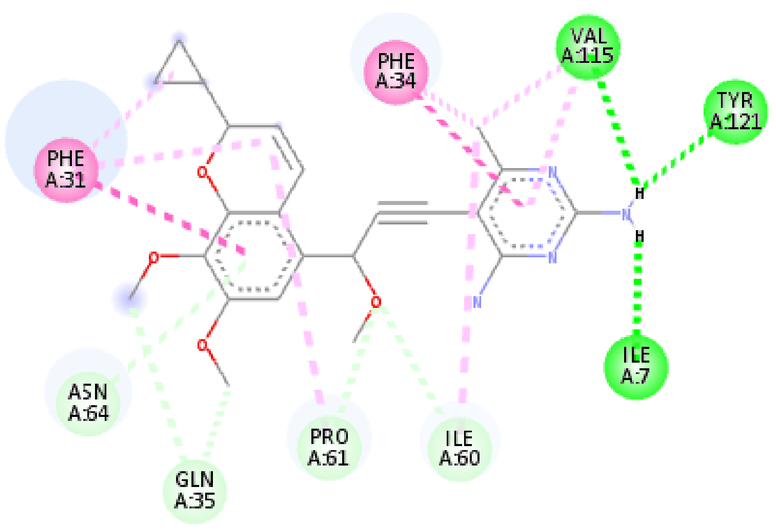
Compounds	R	R_1
1.	-H	-H
2.	$-CH_3$	$-CH_3$
3.	$-CH_3$	-H
4.	$-CH_3$	$-OCH_3$
5.	$-CH_3$	-OH

Table 2. The chemical structures of designed derivatives (2)

Compounds	R	R_1
6.	-H	-H
7.	$-C_2H_5$	-H
8.	$-CH_3$	-H
9.	$-CH_3$	$-OCH_3$
10.	-H	-OH

RESULTS

The designed compounds interacted with the active site of the enzyme, especially with the amino acid residues Phe31A, Phe34A and Asn64A (Scheme 2). Lower binding energy occurs in chromium derivatives, from -9.4 to -8.4 kcal/mol, while compounds containing dimethoxybenzene showed higher binding energies from -8.1 to -7.6 kcal/mol (Table 3). The designed compounds met the criteria for the Lipinski's rule. The presence of diaminopyrimidine ring and propargyl bond in the structure of the compound improves binding to the active site of the enzyme. Based on the results obtained in this study, compound 4 has the most suitable properties as a potential inhibitor of human DHFR.



Scheme 2. Significant interactions of derivative 4 with active site residues of human DHFR

Compounds	Binding energies (kcal/mol)	Hydrophobic interactions	Hydrogen bonds
co-crystallized ligand	-9.0	Phe31, Phe34, Thr56	Arg70, Asn64, Glu30, Gln35
1	-8.4	Phe31	Asn64, Phe31, Phe34, Gln35
2	-9.1	Phe31, Phe34	Asn64, Phe31, Glu30
3	-9.0	Phe31	Asn64, Phe31, Phe34
4	-9.4	Phe31, Phe34	Asn64, Gln35
5	-8.4	Phe34	Phe31, Thr56
6	-7.6	Phe34	Asn64, Phe31
7	-8.1	Phe31, Phe34	Asn64
8	-8.0	Phe34	Phe31, Glu30, Gln35
9	-8.1	Phe34	Phe31, Gln35
10	-7.6	Phe34	Glu30, Thr56

Table 3. Docking scores and key binding interactions of designed derivatives