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IN-SILICO INVESTIGATION OF PYRIMIDINE DERIVATIVE UNVEILING ANTICANCER, ANTIMALARIAL AND ANTIOXIDANT POTENTIAL THROUGH MOLECULAR DOCKING

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ABSTRACT

Pyrimidine derivatives have their wide spectrum of pharmacological properties, making for their therapeutic development. In this study, the in-silico approach was investigated the potential of anti-cancer, anti-malarial and anti-oxidant activity of selected pyrimidine derivative. Molecular docking studies was conducted using SWISSDOCK and other tools to evaluate the binding affinity of these selected compounds against the target protein: Human Cyclin-Dependent Kinase 2(1hck) for anticancer activity, crystal structure of plasmodium falciparum dihydroorotate dehydrogenase(3o8a) for anti-malarial and crystal structure of a mammalian 2-cysperoxiredoxin-HPB23(1qq2) for anti-oxidant activity. The selected compound was also analyzed ADME (Absorption, Distribution, Metabolism and Excretion) properties and drug-likeness using the SWISSADME. The results of several derivative shows strong binding affinity which includes multi-target therapeutic agents.

KEYWORDS: Pyrimidine Derivative, Anticancer, Antimalarial, Antioxidant, Molecular Docking.

INTRODUCTION

Cancer: Cancer is a group of disease characterized by uncontrolled growth and spread of abnormal cells. If the spread of cancer cells this stage is known as metastasis is not controlled, it can result in death. Cancer is caused by many external factors (tobacco, chemical, radiation and infectious organisms) as well as some internal factors (inherited mutations, hormones, immune condition and random mutation). The causes of cancer are diverse, complex and only partially understood.[1]

Malaria: Malaria is a mosquito-borne infectious disease of humans and other animals caused by protists (a type of microorganism) of the genus *Plasmodium*. It begins with a bite from an infected female mosquito, which introduce the protists via its saliva into the circulatory system, and to the liver where they mature and reproduce. The disease causes symptoms that typically include fever and headache, which in severe case can progress to coma or death. The term malaria originates from Medieval Italian: mala aria – "bad air"; the disease was formerly called ague or marsh fever due to its association with swamps and marshland.[2]

Anti-oxidant: Antioxidant are the compounds that protect the cell damage that is caused by free radicals. The free radicals are produced in the body during normal process like breathing, digestion or etc., but their level that increased due to the pollution, stress or any other unhealthy habits. When the free radical forms, they will cause oxidative stress, that can lead to aging and various disease. Antioxidant are helps in neutralizing the free radicals and reduce their harmful effects. The antioxidant properties are naturally found in many fruits, vegetables. In many-case, antioxidant drugs are used to support this defence system, mainly in conditions involving high oxidative stress. These antioxidant drugs help to neutralizing reactive oxygen species (ROS) and prevent the cell and tissue damage. Antioxidant therapy is become important in the treatment of cancer, cardiovascular disorders, neurodegenerative condition, and diabetes.[3]

Pyrimidine: Pyrimidine is a basic heterocyclic aromatic organic compound composed of a six-membered ring with four carbon atoms and two nitrogen atoms at positions 1 and 3. Pyrimidine is a colourless crystalline solid at room temperature. Pyrimidine is an aromatic compound, making it chemically stable and enabling base stacking in nucleic acids. Molecular formula of $C_4H_4N_2$**,** Molar mass of 80.g/mol, Soluble in water, ethanol and organic solvents. The pyrimidine derivatives are used as anti-cancer agent, anti-malarial agent, anti-bacterial agent, anti-oxidant.[4]

Molecular docking: Molecular docking is a computer-based technique used in drug discovery. It helps to understand how a drug attach into a protein present in the body. The main aim of docking is to predict the best position and orientation of the drug that binds inside into the protein's site which is essential in drug discovery. It also calculates a score, which show how strong the binding might be.[5]

Application Of Molecular Docking

Drug Discovery: Helps identify potential drug molecules by predicting how well they bind to target proteins.

Virtual Screening: Rapidly screens large libraries of compounds to find promising drug candidates.

Mechanism of Action: Reveals how drugs interact with proteins at the molecular level.

Lead Optimization: Guides structural changes in compounds to improve binding and activity**.**

Binding Affinity Prediction: Estimate the strength of ligand-protein interaction using binding energy sources.

Enzyme Inhibition Studies: Analysis how inhibitors block enzyme activity by binding to active sites.

Protein-Protein Interactions: Models interactions between two proteins to study signal exchange and disease pathway

Toxicity prediction: Identifies off-target interaction to reduce the risk of side effects.

SOFTWARE USING FOR DOCKING

- AutoDock
- Swissdock
- Flex
- Medock
- Sunflex
- ICM

MATERIAL AND METHODS

Ligand Preparation: (By using Mol inspiration): The 2d Structure of various compound was selected for Anti-cancer, Anti-malarial and anti-oxidant. By using the Mol inspiration online software high quality ligand is prepared and the ligands 2d or 3d were obtained at the software. The ligand is prepared by sketching individual design in mol inspiration and then copy the smile to proceed for further steps in SWISSDOCK.[6]

Protein Preparation: (By using Protein Data Bank-RCSB): The Protein Data Bank (PDB) is a three-dimensional structural database for large biological molecules including proteins and nucleic acid. The data, which usually obtained by X-ray crystallography, NMR spectroscopy or increasingly, and submitted by biologist and biochemist from all over the world, is free accessible on the Internet through the websites of its member organisation. The RCSB (Research Collaboratory for Structural Bioinformatics) protein data bank is an online software which contains the 3d structure of biological molecule like protein, DNA. The protein is selected and entered into the SWISS Dock and the protein is prepared. The protein such as 1hck for Cancer activity, 3o8a for Malarial activity and 1qq2 for anti-oxidant activity were selected. And used in the Docking of the selected activity.[7]

ADME Analysis: The ADME properties of the selected molecule is calculated by the Swiss ADME. The smile that copy from mol inspiration is used in SWISS ADME to calculate the ADME properties. It predicts the drug-likeness, physiochemical properties like formula, molecular weight, No. of heavy atoms, No. H-bond donors, No. of H-bond acceptors, molar refractivity, TPSA (topical polar surface area). ESOL solubility, ESOL Log S, ESOL Class, Ali Log S, Ali Solubility, Ali Class, Silico-IT Log S, Silico-IT Solubility, Silico-IT class. The Pharmacokinetics compounds include GI absorption, BBB permeation, Pgp-substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitors, Log Kp (skin Permeation). The predicted drug-likeness compounds include Lipinski, Ghose, Veber, Egan, Mugge, Bioavailability, PAINS, Brenk, Leadlikeness, synthetic accessibility.[8]

Docking Analysis: The structure of the target protein, as well as the ligand can automatically prepared for docking in SWISSDOCK (a docking web server). The seamless visualisation significantly aids the analysis of docking. A docking can be started in just three steps using SWISSDOCK web interface: user must identify the protein, prepare the ligand and analysis

the docking parameter, and then start the docking to analysis the compound and protein binding affinity.[9]

RESULT AND DISCUSSION

SWISSDOCK molecular docking software did the docking studies of the ligands to active target site of protein to determine compounds binding energy. In this study, we have collected 20 selected compounds of pyrimidine. They were examined to recognize the prospects of selected compounds that can act as a drug against anti-cancer, anti-malarial and anti-oxidant disease causing agents. That all selected compounds are mentioned in table 1.

Table 1: compound number and IUPAC name.

SI. no	COMPOUND NUMBER	IUPAC NAME
1.	Compound-01[10]	6-(2-methylphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile
2.	Compound-02[10]	4-[(4-acetylphenyl) amino]-6-(2-methoxyphenyl)-2-thioxo-1,2-dihydropyrimidine-5-Carbonitrile
3.	Compound-03[10]	4-hydrazino-6-(2-methylphenyl)-2-thioxo-1,2-dihydropyrimidine-5-Carbonitrile
4.	Compound-04[11]	8-bromo-5-chloro- [1,2,4] triazolo [4,3-c] pyrimidine-3-amine
5.	Compound-05[11]	5-bromo-2-chloro-4-(3,5-dimethyl-1Hpyrazol-1-yl)-pyrimidine
6.	Compound-06[11]	8-bromo-5-chloro-3- methyl [1,2,4] triazolo [4,3-c] pyrimidine
7.	Compound-07[12]	2-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)- pyrimidine
8.	Compound-08[12]	n-chloro acetyl- 2-amino-4-(2,4-dichloro-5-fluoro phenyl) 6-(aryl)-pyrimidine
9.	Compound-09[13]	1-(6-Methyl-4-(naphthalen-1-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethanone
10.	Compound-10[14]	N^4, N^6-bis(4-chlorobenzylidene)-2-(2-methoxyethylsulfanyl)-3,4-dihydropy rimidine-4,6-diamine
11.	Compound-11[15]	2-Isopropyl-6-methylpyrimidin-4-yl-3,4,5-trimethoxybenzoate
12.	Compound-12[16]	2-[(2E)-2-(4-fluorobenzylidene)hydrazino]-4-(1H-indol-3-yl)-6 oxo-1,6-dihydropyrimidine-5-carbonitrile
13.	Compound-13[17]	4-(Anthracen-9-yl)-6-(furan-2-yl) pyrimidin-2-amine
14.	Compound-14[14]	6,8-bis-(benzylidene-amino)-3,4,6-trihydropyrimido2,1-b 1,3thiazin-2-one
15.	Compound-15[18]	6-(4-chlorophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol 1-yl)-1,6-dihydropyrimidine-2-thiol
16.	Compound-16[19]	2-[(2Z)-2-benzylidenehydrazinyl]-4-(4-methoxyphenyl)-6-(thiophen-2-yl) pyrimidine
17.	Compound-17[20]	2(4,5Dihydro3phenyl5(thiophen2yl) pyrazol1yl)4(4-methoxyphenyl)6(thiophen2yl) pyrimidine
18.	Compound-18[20]	7-(4-methoxphenyl)-3-methyl-5-(thiophen-2-yl) [1,2,4] triazolo[4,3-

		a] pyrimidine
19.	Compound-19[10]	7-(2-methoxyphenyl)-3-oxo-5-thioxo-2,3,5,6 tetrahydro[1,2,4]-triazolo[4,3-c] pyrimidine-8 carbonitrile
20.	Compound-20[10]	8-(2-methoxyphenyl)-3,4-dioxo-6-thioxo-3,4,6,7 tetrahydro-2h-pyrimido[6,1-c] - [1,2, 4] triazine-9 carbonitrile

ADME Study Report

The selected compounds were then subjected to ADME testing using SWISSADME software. The ADME property of various compounds are based on their structure, functional groups and molecular properties such as Molecular Weight (MW), BBB permeant (Blood-Brain Barrier parameter of compounds), GI (Gastrointestinal absorption), H-bond acceptors, H-bond donors, Violation and MLogP (Moriguchi octanol-water partition coefficient) are shown in the table-2.

Table 2: ADME Study report.

Compound No.	M. W/mol	BBB	GI Absorption	H-bond acceptors	H-bond donors	Violations	M Log p
C-1	243.29g/mol	No	High	2	20	0	1.01
C-2	376.44 g/mol	No	Low	4	2	0	1.26
C-3	257.32 g/mol	No	High	3	3	0	0.66
C-4	248.47 g/mol	No	High	3	1	0	1.16
C-5	287.55 g/mol	Yes	High	3	0	0	2.08
C-6	247.48 g/mol	Yes	High	3	0	0	1.91
C-7	348.21 g/mol	Yes	High	3	1	0	4.12
C-8	424.69 g/mol	NO	High	4	1	0	3.86
C-9	296.39 g/mol	Yes	High	1	2	0	2.10
C-10	447.39 g/mol	NO	High	4	1	0	3.42
C-11	346.38 g/mol	No	High	7	0	0	1.72
C-12	372.36 g/mol	No	High	5	3	0	2.06
C-13	337.38 g/mol	No	High	3	1	0	2.70
C-14	374.47 g/mol	No	High	4	0	0	2.37
C-15	443.96 g/mol	No	High	3	1	1	4.67
C-16	386.48 g/mol	No	High	4	1	0	3.02
C-17	494.64 g/mol	No	Low	4	0	0	4.09
C-18	322.39 g/mol	No	High	4	0	0	2.29
C-19	327.32 g/mol	No	Low	5	2	0	0.22
C-20	299.31 g/mol	No	High	4	2	0	0.45

The Molecular Docking Result of Selected Pyrimidine Derivative

The docking studies of the ligands to protein active were done by modern molecular docking programme SWISSDOCK to determine the compounds binding affinity are shown in the table-3.

Table 3: The molecular docking result of selected pyrimidine derivatives.

SI. NO	COMPOUNDS	PROTEIN ID		
		Anti-cancer (1HCK)	Anti-Malarial (3O8A)	Anti-oxidant (1QQ2)
1.	Compound-1	-7.3194	-7.5208	-6.1373
2.	Compound-2	-8.1104	-8.1552	-6.9336
3.	Compound-3	-7.5645	-7.9464	-6.3976
4.	Compound-4	-6.5064	-6.7074	-6.5405
5.	Compound-5	-6.7959	-6.4536	-7.0231
6.	Compound-6	-6.2636	-6.4864	-6.3964
7.	Compound-7	-7.4161	-7.8297	-6.2143
8.	Compound-8	-7.6619	-7.4106	-6.6447
9.	Compound-9	-7.4291	-7.1707	-7.3712
10.	Compound-10	-8.0604	-8.7489	-7.8081
11.	Compound-11	-7.6899	-7.3564	-6.7962
12.	Compound-12	-8.0137	-8.1475	-6.9232
13.	Compound-13	-8.0048	-7.6995	-6.4745
14.	Compound-14	-7.9394	-8.0912	-7.2272
15.	Compound-15	-8.2180	-7.2934	-7.3303
16.	Compound-16	-7.8437	-8.4914	-6.7940
17.	Compound-17	-8.3874	-8.0339	-7.3475
18.	Compound-18	-7.3271	-8.4695	-6.6584
19.	Compound-19	-7.4919	-7.4732	-6.5447
20	Compound-20	-7.1419	-7.4261	-6.2599
21	5-Fluorouracil Anti-Cancer Agent	-5.5997	-	-
22	Pyrimethamine Anti-Malarial Agent	-	-7.0782	-

CONCLUSION

The present in-silico investigation successfully explored the anti-cancer, anti-malarial and antioxidant potential of various pyrimidine derivatives using molecular docking approaches using SWISSDOCK. The selected compounds show a good binding affinities towards the target proteins associated with each activity.

In the anti-cancer protein (1hck), the compounds such as Compound-17 (-8.3874 kcal/mol), Compound-15(-8.2180kcal/mol), compound-02(-8.1104 kcal/mol Compound-10(-8.0604kcal/mol) and Compound-12(-8.0137kcal/mol) show the binding affinity more than-**8.00 kcal/mol.**

In anti-malarial protein(3o8a)- Compound-10(-8.7489 kcal/mol), Compound-16 (-8.4914 kcal/mol), Compound-18 (8.4695 kcal/mol), Compound-2 (-8.1552 kcal/mol) and Compound-12 (-8.14755 kcal/mol) show the binding affinity more than **-8.00 kcal/mol.**

In anti-oxidant protein (1qq2); compounds such as Compound-10 (-7.8081 kcal/mol), Compound-9 (-7.3712 kcal/mol), Compound-17(-7.3478), Compound-15(-7.3303 kcal/mol) and Compound-14(-7.2272 kcal/mol) show the binding affinity more than **-7.00 kcal/mol.**

However, the standard drug of anti-cancer agent (5-Fluorouracil) shows **-5.5997 Kcal/mol** in 1HCK protein and the standard drug for anti-malarial agent (Pyrimethamine) shows **-7.0782 Kcal/mol** in 3O8A.

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