American Journal of Medicine and Public Health

Mini Review
Published: 05 Jan, 2022

Insilco Molecular Annotation of Pyrimidine Derivatives and Their Interaction Study with Protease 1UK3 of COVID-19

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Abstract

The heterocyclic compounds are plentiful in nature and are biologically important class of compounds to living things because most of the natural and non-natural products contain heterocyclic structure. Many heterocyclic compounds exhibit useful biological activities. However synthetic drugs and synthetic dyes enclose heterocyclic ring structure as well as the natural products for example vitamin, hormones, antibiotics, amino acids, hemoglobin and alkaloids. Various synthetic heterocyclic compounds such as pyrimidines, pyridine, pyrrole, Indole, Triazole, pyrrolidine, thiophene, thiazole, furan, piperidine, oxazole and pyrazole exhibit significant biological importance.

Keywords: Pyrimidine derivatives; Protease 1UK3; COVID-19

Introduction

Nitrogen containing heterocycles are medicinally important class of compounds from the family of heterocyclic compounds and they have contributed to the society from the medicinal and industrial point of view which helps to know life processes [1-3]. Hence, researchers have attracted and substantial attention in the designing of biologically active molecules [4,5]. Pyrimidine is nitrogen containing six-membered heterocyclic organic compound consists of 4 carbon and 2 nitrogen atoms at positions 1 and 3 of the six membered ring. It is one of the isomeric forms of three forms of diazine. For drug designing pyrimidine is promising structural moiety. Most of the properties of pyrimidine are common with the pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier.

However, the pyrimidine compounds are more significant and effective antimicrobial agents and present throughout the nature. These compounds are the building blocks of various natural products such as vitamin, antibiotics and liposaccharides. In nucleic acid chemistry pyrimidine structure is prominent. In our daily life naturally occurring pyrimidine compounds have enormous importance. The fundamental building blocks for DNA (Deoxyribonucleic Acid), RNA (Ribonucleic Acid) and Vitamin B1 (thiamine) are pyrimidine derivatives such as adenine, guanine, cytosine, thymine and uracil. In many biological processes such as antibiotics, anti-bacterial, nucleoside, cardiovascular compounds the pyrimidine compounds found to plays important role. On this basis, in the design and discovery of pharmacologically active compounds and physiologically new compounds the heterocyclic compounds play important role which helps to discover new drugs [6]. Literature discloses that these compounds have more potential and interest in practical aspects. Medicinal chemistry practices are devoted for discovery as well as development of new pharmaceutical agents used for curing diseases [7]. The nucleic acid are essential constituent of all cells and thus of all living matter cytosine is found to be present in both types of nucleic acids i.e. Ribonucleic Acid (RNA) and Deoxyribonucleic Acid (DNA) while uracil present only in RNA and thymine only in DNA.

Review of Literature

The pyrimidine heterocyclic scaffolds have received considerable attention due to interesting pharmacological properties. The point of interest in this study is to design and synthesize compounds comprising of the bioactive pharmacophores and an attempt has been made to design and explore the optimal structure requirement for the potential biological activity. Pyrimidine has extensive spectrum of biological activities (Figure 1) such as anti-inflammatory [8,9], antimicrobial [10], antitubercular [11], anti-HIV [12], anti-tumor [13], anti-malarial [14], diuretic [15], anti-

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Received Date: *08 Dec 2021*
Accepted Date: *27 Dec 2021*
Published Date: *05 Jan 2022*

Citation:
Ashish Gulwe B, Sachin B Jadhav. Insilco Molecular Annotation of Pyrimidine Derivatives and Their Interaction Study with Protease 1UK3 of COVID-19. Am J Med Public Health. 2022; 3(1): 1029.

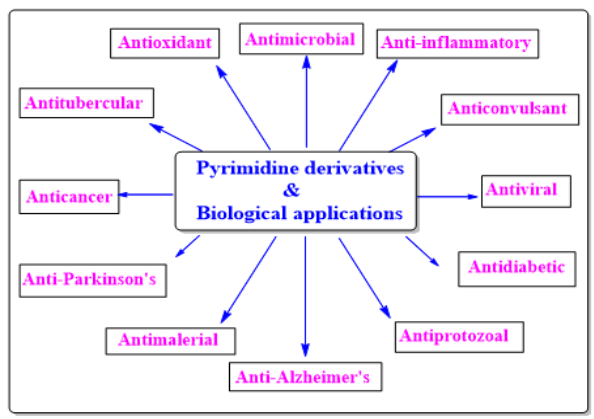

Figure 1: Biological activities of pyrimidine derivatives.

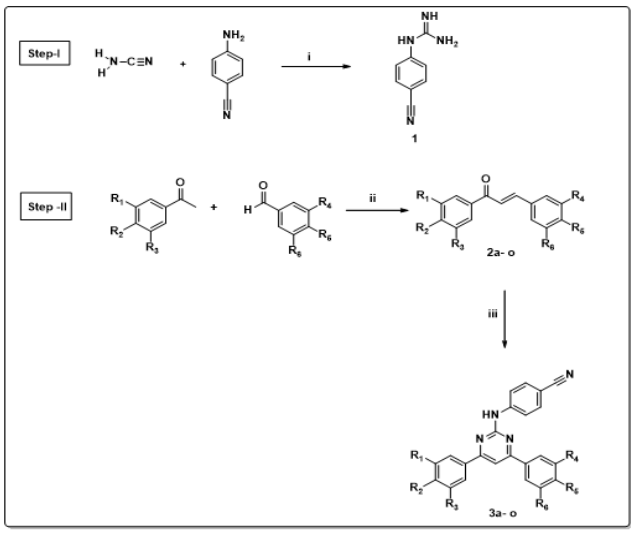

Figure 2: Synthesis of 4-(4, 6-diphenyl pyrimidin-2-ylamino) benzonitrile.
Reagents and conditions: (i) 5% Aq. HCl, heat for 4 h to 5 h and 20% Aq. NaOH solution (for neutralization); (ii) NaOH, ethanol, stir at rt for 10-12 h; (iii) N-Cyanophenyl guanidine (1), NaOH, ethanol, reflux for 5 h to 6 h.

Table 1: Derivatives with various substituents and its physical data.

Sr. No.	Product	Substituent's						MP °C	Yield %
		R_1	R_2	R_3	R_4	R_5	R_6		
1	3a	H	Cl	H	H	H	H	210	80
2	3b	H	F	H	H	NO_2	H	201	77
3	3c	H	OCH_3	H	H	F	H	211	81
4	3d	H	Cl	H	H	F	H	232	78
5	3e	H	F	H	H	F	H	219	85
6	3f	H	CH_3	H	H	Br	H	296	79
7	3g	H	F	H	H	H	H	179	76
8	3h	H	CH_3	H	H	F	H	177	78
9	3i	H	CH_3	H	OCH_3	OCH_3	OCH_3	221	80
10	3j	H	F	H	OCH_3	OCH_3	OCH_3	249	83
11	3k	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	204	76
12	3l	H	CH_3	H	H	Cl	H	219	79
13	3m	H	Cl	H	H	Cl	H	274	85
14	3n	H	OCH_3	H	OCH_3	H	H	197	80
15	3o	H	OCH_3	H	OCH_3	OCH_3	OCH_3	220	79

Table 2: It comes to the conclusion that C23H16N4O6 this molecule has most significant energy of -14.1 kcal/mol.

Sr No	Molecular Formula	Molecular weight	No of heavy Atoms	H bond Acceptors	H Bond Donors	Lipinski #violations	Binding Energy (Kcal/ Mol)
1	**C23H16ClN4**	383.85	28	3	1	0	-10.7
2	**C24H17FN5O2**	426.42	32	6	1	0	-13.1
3	**C24H18FN4O**	397.42	30	5	1	0	-10.5
4	**C23H15ClFN4**	401.84	29	4	1	1	-11.1
5	**C23H15F2N4**	385.39	29	5	1	1	-10
6	**C24H18BrN4**	442.33	29	3	1	1	-10.8
7	**C23H16FN4**	367.4	28	4	1	0	-10.6
8	**C24H18FN4**	381.42	29	4	1	0	-12.8
9	**C24H18N4O3**	410.42	31	6	4	0	-10.6
10	**C23H15FN4O3**	414.39	31	7	4	0	-10.8
11	**C29H28N4**	432.56	33	3	1	1	-10.9
12	**C23H16N4O6**	**444.4**	**33**	**9**	**7**	**1**	**-14.1**
13	**C23H14Cl2N4**	417.29	29	3	1	1	-11.1
14	**C23H16N4O2**	380.4	29	5	3	0	-10.7
15	**C23H16N4O4**	412.4	31	7	5	0	-10.7

neoplastic [16], cardiovascular [17] etc. Pyrimidine compounds have application in hypnotic drugs for the nervous system (Table 1 and Figure 2). ADMET prediction and binding free energy when docked with protease 1UK3 of protease of COVID-19. From the Table 2 it comes to the conclusion that C23H16N4O6 this molecule has most significant energy of -14.1 kcal/mol.

Results

The docking experiment is performed using PyRx 0.8 version the results shows that after docking the above molecules the most significant binding free energy is for the C23H16N4O6 this molecule it follows the Lipinski Rule of 5 has molecule weight as 444.4, no of heavy atoms 33, no of H Bond acceptors as 09, no of hydrogen bond donors 7, Lipinski is rule of 5 violation 1, binding free energy -14.1 kcal/mol. So this is the best inhibitor of the protease of the COVID-19 virus among other pyrimidine derivative.

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