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In-Silico Approach of Pyrimidine Derivatives Inhibitor of BRD4 as a Potent Anticancer Agent

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ABSTRACT

Series of novel pyrimidine derivatives compound were designed with the help of chemsketch software, all the designed compound were screened and docked with Bromodomain containing protein (BRD4) which was downloaded from protein data bank with their unique PDB Id 4HY3 for its anti-cancer activity using Accelrys drug discovery studio 3.5.Molecular docking was performed for 22 designed ligands against inhibition towards BRD4 and finally compared with the standard inhibitor (JQ1). Some of the designed compounds possess good binding affinity towards BRD4. This designed compound interacts with various amino acids which include ARG16, SER83, ILE 21. Among all designed compound, **2c** was found to possess good CDOCKER interaction energy, ADME parameters, virtual toxicity and Lipinski Rule of 5. Therefore it was predicted that these pyrimidine derivatives compound could be effective in drug discovery for cancer treatment. Rational behind the work is to know best selective inhibitor of BRD4 with our designed pyrimidine derivatives compound. The significance of this study is to find out more promising molecule for anticancer activity.

INTRODUCTION

Cancers are produced by cells via different exposure like radiation, smoking habits, and other phenomena and that does not have its control and behave mad. Normal cells are the sanest things in the world. They are polite and enjoy the company of other cells.[1]

Pyrimidine consist of a six-membered heterocyclic compound having two N-atoms in the ring constitutes a significant component of nucleic acid, and used as a pharmacophore for the synthesis of many drugs i.e., anticancer, antiviral and antibacterial agents.[2] The pyrimidine derivatives anticancer drug were developed based on a modification of the core structure of the compound with different substitution moieties, conjugation with different compound and coordinated with metal ions and show the potential scaffold for the biological activities with novel compound.[3]

Bromodomain-containing protein 4 (BRD4) is a chromatin reader protein, which includes BET family-like BRD2, BRD3, BRD4, and BRDT, Among all, the most challenging BET family proteins are BRD4 that get interacted with N-acetyl lysine residues on histones and nuclear proteins via two conserved N-terminal.[4-7] BRD4 get interacted with acetylated chromatin protein to discrete the function of the genomic region and to regulate mediator complex such as pTEFb via RNApol II, elongation and transcription mechanism.[8-9] several acetylated transcription factors get involved such as RelA, ERα, p53, and TWIST to maintain the oncogenic gene expression in cancer.[10-12] In a healthy body, BRD4 protein is required to maintain the chromatin stability, controls, and regulate the cell cycling transition from M phase to G1 phase via the recruitment of P-TEFb mediator complex.

The *in vivo* study indicates the defects in cell differentiation and organogenesis of heterozygous Brd4+/- as the null animal dies in utero therefore, for the normal cell cycling progression and development, the BRD4 is most required.[13] The epigenetic modification does not change the sequence of nucleotide but reversible change and heritable alter to the DNA of a cell. Several epigenetic mechanisms are get involved in maintaining normal cellular homeostasis and normal gene expression via changes in CpG island methylation patterns and histone modifications the dysregulation of proteins lead to disease pathogenesis via the interaction with modified DNA macro-molecular complexes. [14-15]

2. MATERIALS AND METHOD:

Docking program requires three computation steps to carry out docking study these are as follows:

(1) Preparation of the receptor

(2) Preparation of the ligand

(3) Setup of the parameters of the docking program

The following subsections describe these three steps in detail.

2.1. RECEPTOR PREPARATION:

The three-dimensional structure of BRD4 (PDB CODE-4HY3) was obtained from PDB. (http://www.rcsb.org/pdb/home/home.do). RCSB is a single, global archive for information about the 3D structure of macromolecules such as protein, DNA and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy.[16]

2.2. LIGAND PREPARATION:

The pyrimidine derivative compound was designed with help of ChemDraw and the ligand was loaded into Accelrys drug discovery studio 3.5. To predict the ligand molecular properties e.g. a log P value, hydrogen bond donors and hydrogen acceptors, surface area and molecular weight, absorption, distribution, metabolism (ADME) and analyses for solubility, intestinal absorption excretion, and toxicity.

High throughput screening approaches and virtual screening were used for the identification of lead compounds. The compound datasets were screened effectively in the initial stages for ADMET to decrease cost and clinical failures of new drugs.[16]

2.3. DRUGS LIKENESS EVALUATION:

Drug likeness properties of the compound were predicted with the help of Lipinski drug filter using Accelrys drug discovery studio 3.5. The prediction of the Lipinski rule gives us a concept regarding the proper use of the commercial drug. [16]

2.4. ADME DESCRIPTORS:

Absorption, distribution, metabolism, and excretion is an important parameter used to know the pharmacokinetic properties of the drugs, as well as the degree of hepatotoxicity and plasma protein binding (PPB) aqueous solubility, blood-brain barrier (BBB) and CYP2D2 that tells us the simple concept of the proper use of drugs.[16]

2.5. MOLECULAR SIMULATION STUDIES:

Chemistry at Harvard Molecular Mechanics (CHARMM) force field is a flexible molecular mechanics and dynamics program that is used in drug Accelrys drug discovery studio 3.5. For ligand minimization and protein minimization, broad range calculations such as calculation of geometries, interaction and conformation energies, local minima, barriers to the rotation, free energy time-dependent dynamic behavior, and simulations.[16]

2.6. TARGET PROTEIN AND ACTIVE SITE PREDICTION:

The various literature surveys were taken into consideration for the evaluation of protein and the active sites.

2.7. MOLECULAR DOCKING:

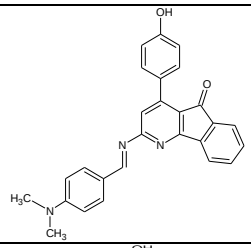
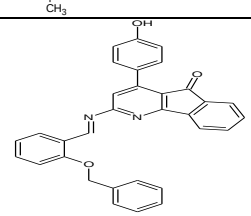
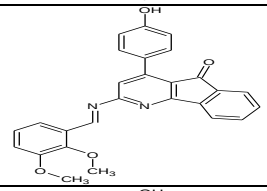
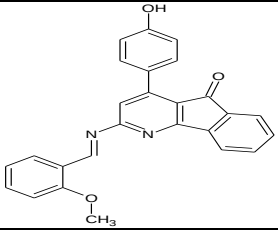
To carry out the docking study, drug discovery studio 3.5 is used. In this study, the ligand was designed using chem sketch/ChemDraw, and protein was downloaded from the protein data bank (PDB) with the link (http://www.rcsb.org/pdb/home/home.do). E.g. to download bromodomain protein 4HY3 is the PDB code. Hydrogen was added to interact with amino acid present in the particular protein which is seen in the 2D structure. To add the hydrogen click on chemistry then hydrogen adds. Both the ligand and protein should be prepared. The ligand was prepared on clicking small molecule followed by prepare ligand and then ligand minimization was done. Protein preparation was done on clicking macromolecules then prepare protein followed by full minimization of protein once both the ligand and protein were prepared the click on receptor-ligand interaction, List will be displayed, click on define and editing binding sites, click on receptor cavities click on docking ligand (C-Docker), Box will appear (In parameter value), Input receptor = 4hy3, Input ligand = add all the ligand. Click on run.[16]

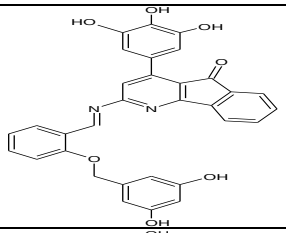
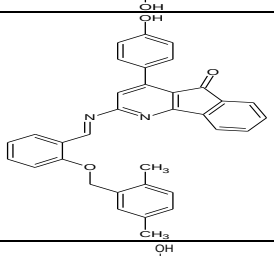
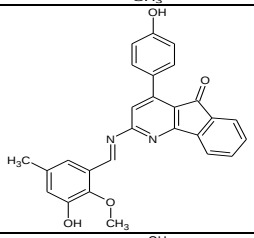
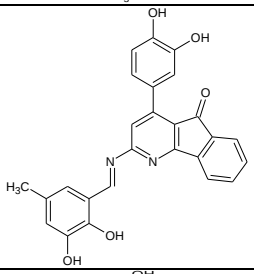
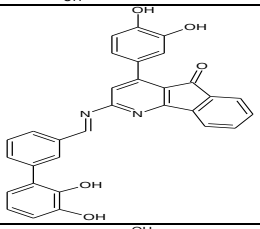
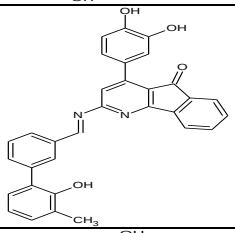
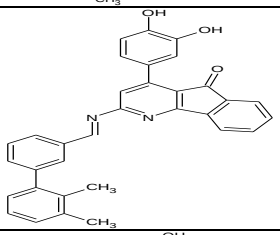
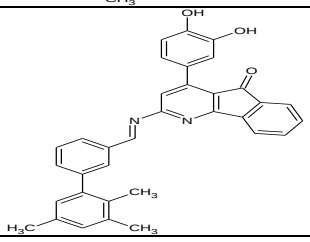
3.0 RESULTS AND DISCUSSION:

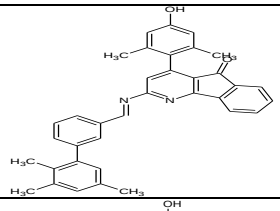
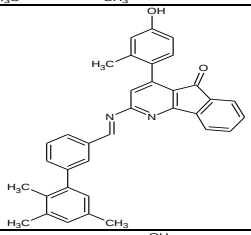
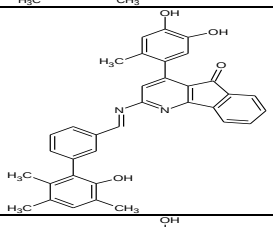
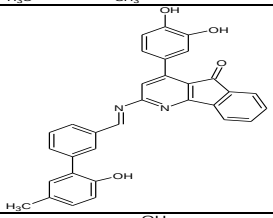
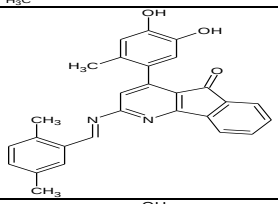
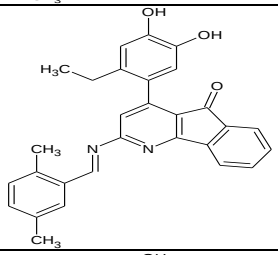
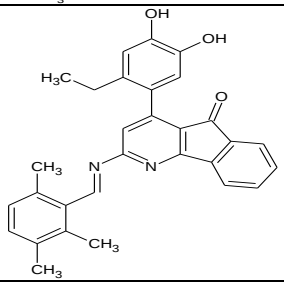
3.1. Drug Likeness:

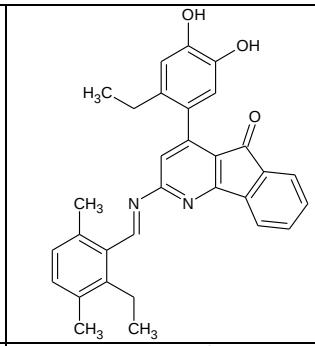
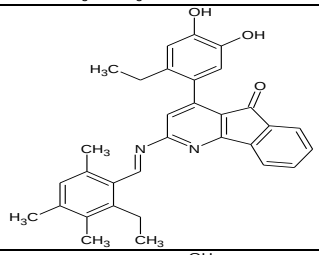
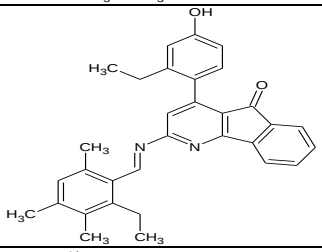
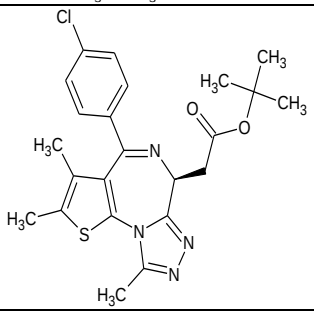
The pyrimidine derivative designed compound having a good number of hydrogen bond acceptors and donors. The hydrogen bond donor ranges from 0 to 5 whereas acceptor having 3 to 8. The compound was designed to enhance the binding with the receptor using hydrogen bonding, all the pyrimidine derivative designed compound follow the Lipinski rule of 5 and increases the drug-likeness properties that are mention in **Table 1** polar surface areas were taken into consideration to know the amount of drug to permeate through the cell membrane. All pyrimidine derivatives designed compound are within the permissible limit and having no bioavailability problem.

Table No. 1: Drug likeness

Compound code	Compound structure	No of H Bond donor	No of H Bond acceptor	A log Å	Molecular Weight	Molecular Fractional polar Surface areas
2a		1	5	5.77	419.47	0.16
2b		2	4	7.07	483.53	0.16
2c		2	5	5.47	437.46	0.20
2d		2	4	5.49	407.44	0.19

2f		5	8	5.40	546.52	0.31
2g		2	4	8.04	511.59	0.15
2h		3	5	5.73	437.46	2h
2i		5	6	5.26	439.43	0.30
2j		5	6	6.30	501.50	0.27
2k		4	5	7.02	499.53	0.22
2l		3	4	7.75	497.56	0.18
2m		3	4	8.24	511.51	0.17

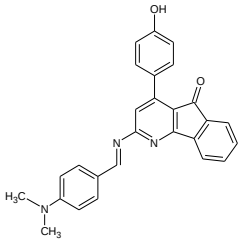
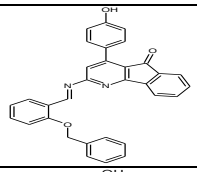
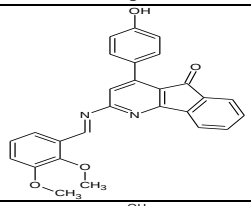
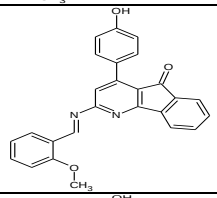
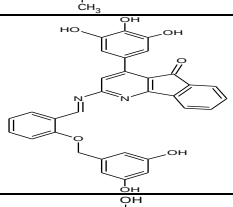
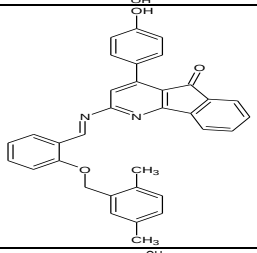
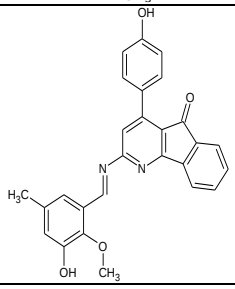
2p		2	3	9.45	523.64	0.12
2q		2	3	8.97	509.61	0.13
2r		4	5	8.48	541.61	0.20
2s		4	5	7.02	499.53	0.22
2t		3	4	6.72	435.49	0.20
2u		3	4	7.18	449.52	0.19
2v		3	4	7.66	463.54	0.18

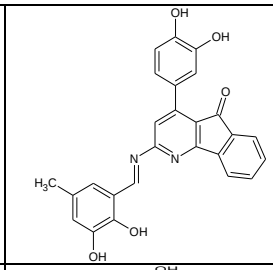
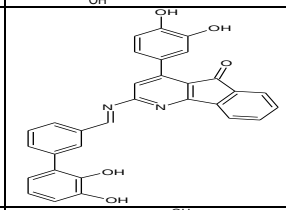
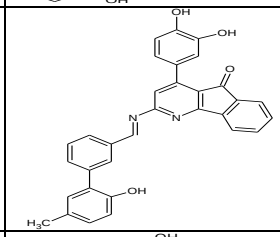
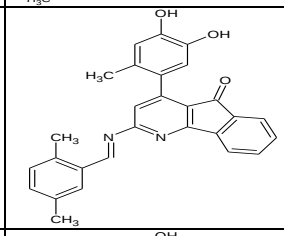
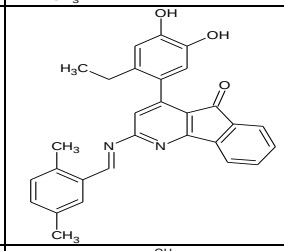
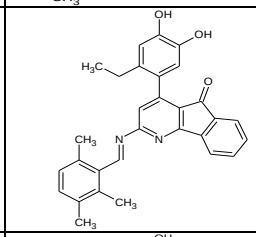
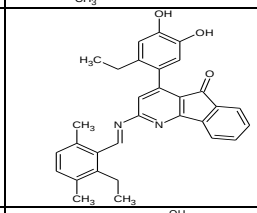
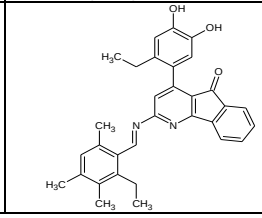
2w		3	4	8.12	477.57	0.17
2x		3	4	8.61	491.61	0.17
2y		2	3	8.85	475.60	0.13
JQ1		0	5	4.95	456.98	0.21

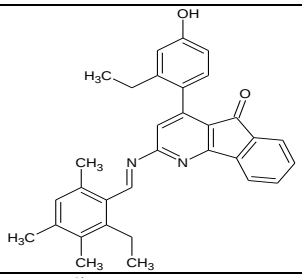
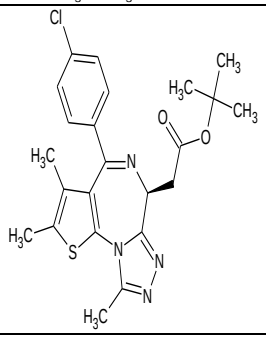
3.2. ADME INVESTIGATION:

Accelrys drug discovery studio 3.5. was used to calculate *in silico* ADME parameters. They were calculated to avoid the failure of the drug in the final stages of the discovery process. All the 22 designed compounds possessed absorption level in the range of 0 and 1 which indicates that the designed compounds possessed good to moderate absorption. The aqueous solubility level and blood-brain barrier (BBB) level were in the range of 1-4 indicating that the designed compounds possessed optimal solubility with undefined BBB level. The inhibition level of CYP2D6 and hepatotoxic level was less than 1. All these indicated that the designed compounds could be druggable and hence it was further processed for docking studies. The details of the ADME investigation were specified in **Table 2.**

Table No. 2: ADME investigation of the designed compounds

Compound code	Compound structure	Aqueous solubility Level	BBB Level	CYP2D6	Hepatotoxicity Level	PPB Level
2a		1	4	-1.50	4.54	4.23
2b		1	4	-1.41	-1.67	2.11
2c		1	4	-1.95	2.75	3.56
2d		1	1	-0.70	2.04	2.98
2f		1	4	-1.07	2.01	0.26
2g		0	4	0.28	-0.31	3.49
2h		1	4	-2.74	2.02	3.06

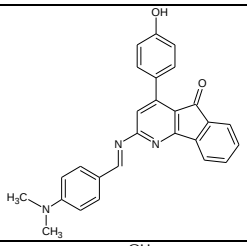
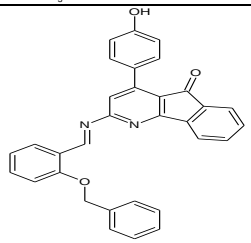
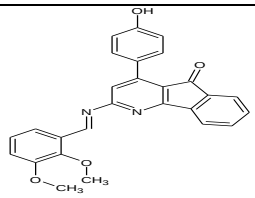
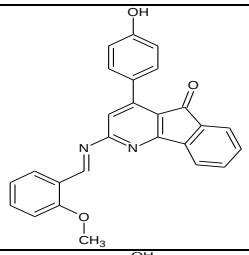
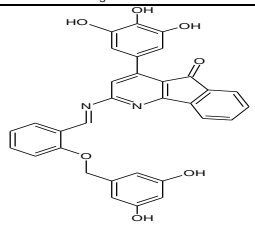
2i		1	4	-2.62	3.01	2.65
2j		1	4	-1.99	4.33	1.99
2s		1	4	-2.01	2.95	1.87
2t		1	4	-1.36	2.21	3.29
2u		1	4	-1.61	1.35	3.89
2v		1	4	-1.39	1.23	3.32
2w		0	4	-1.22	2.11	2.57
2x		0	4	-1.42	2.12	2.36

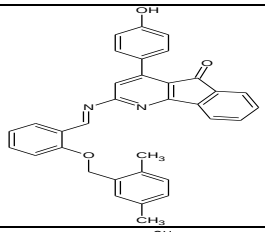
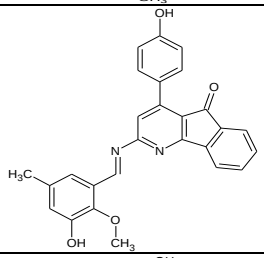
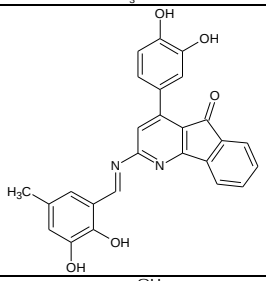
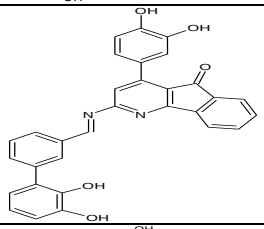
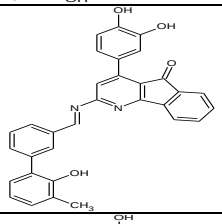
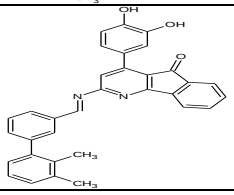
Compound code	Compound structure	Aqueous solubility Level	BBB Level	CYP2D6	Hepatotoxicity Level	PPB Level
2y		0	4	-0.58	1.71	2.52
JQ1		1	1	-5.26	-1.57	12.21

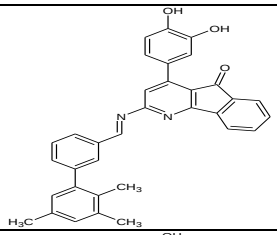
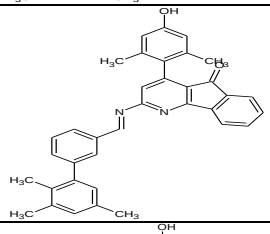
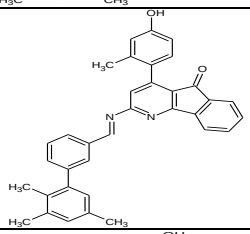
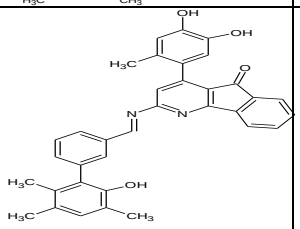
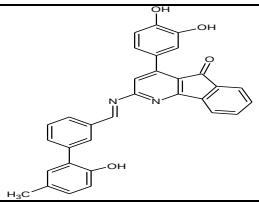
3.3. VIRTUAL TOXICITY STUDIES:

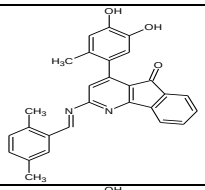
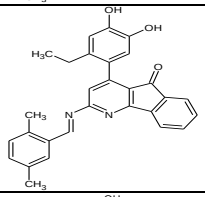
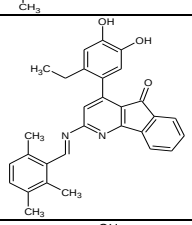
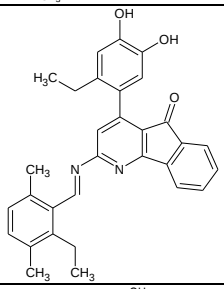
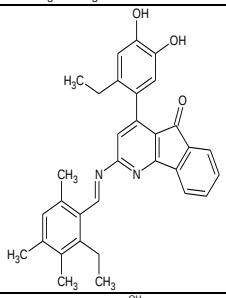
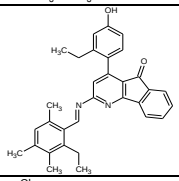
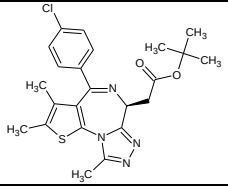
TOPKAT predicts endpoint of toxicity based on chemical structure in Accelrys drug discovery studio 3.5. including NTP carcinogenicity (female Rat, Male Rat), Ames Mutagenicity, Rat Oral LD_{50}, Skin irritation and development of toxicity shown in **Table 3:** The various model were computed and recorded that satisfied all the validation criteria for the query compound that are show in the table number 3. The mutagenicity predict the drug's potential to cause human cell to mutate, which is based on Ames research carcinogenicity assay and estimate the compound potential to cause normal human cell to get cancer, the toxicity studies was carried out for both the male and female rat to reduce the time and cost in the clinical trial. The skin irritation test support the topical use of particular compound the compound predicted to be non-toxic if it ranges from 0 to 0.29, between 0.3 to 0.69 the compound is indeterminate and if it ranges from 0.7 and 1 is toxic. If the discriminant score is negative then probability of causing cancer is 0 or non-carcinogenicity in case, the discriminant score is positive the probability to getting cancer is high.

Table No. 3a: Toxicity Studies

Compound Code	Compound Structure	Aerobic Biodegradability probability	Aerobic Biodegradability prediction	Rat Inhalation LC_{50}	Rat Maximum Tolerated Dose feed
2a		0.03	Non-Degradable	3.09	0.17
2b		0.25	Non-Degradable	4.28	0.31
2c		0.22	Non-Degradable	9.96	0.19
2d		0.23	Non-Degradable	12.29	0.20
2f		0.21	Non-Degradable	0.70	0.77

Compound Code	Compound Structure	Aerobic Biodegradability probability	Aerobic Biodegradability prediction	Rat Inhalation LC_{50}	Rat Maximum Tolerated Dose feed
2g		0.15	Non-Degradable	8.21	0.24
2h		0.13	Non-Degradable	8.74	0.25
2i		0.11	Non-Degradable	4.22	1.21
2j		0.19	Non-Degradable	1.70	1.33
2k		0.16	Non-Degradable	5.95	0.72
2l		0.11	Non-Degradable	8.89	0.45

Compound Code	Compound Structure	Aerobic Biodegradability probability	Aerobic Biodegradability prediction	Rat Inhalation LC_{50}	Rat Maximum Tolerated Dose feed
2m		0.09	Non-Degradable	8.35	0.43
2p		0.11	Non-Degradable	11.71	0.26
2q		0.09	Non-Degradable	12.47	0.27
2r		0.10	Non-Degradable	4.92	0.61
2s		0.142104	Non-Degradable	5.95	0.726415

Compound Code	Compound Structure	Aerobic Biodegradability probability	Aerobic Biodegradability prediction	Rat Inhalation LC_{50}	Rat Maximum Tolerated Dose feed
2t		0.17	Non-Degradable	9.42	0.48
2u		0.12	Non-Degradable	16.20	0.53
2v		0.11	Non-Degradable	15.27	0.51
2w		0.12	Non-Degradable	14.29	0.54
2x		0.36	Non-Degradable	13.44	0.51
2y		0.09	Non-Degradable	21.35	0.34
JQ1		0.09	Non-Degradable	1.12	0.01

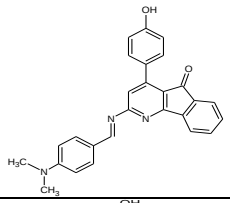
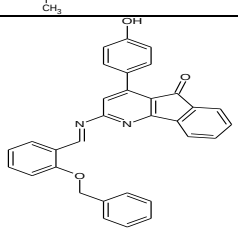
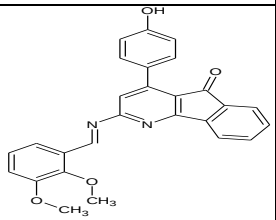
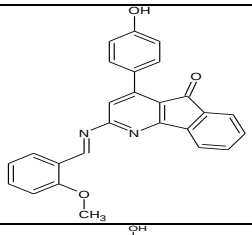
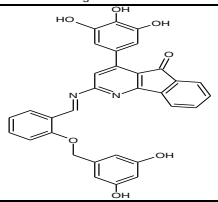
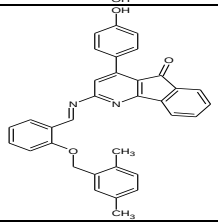
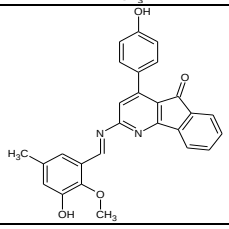
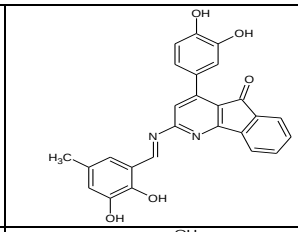
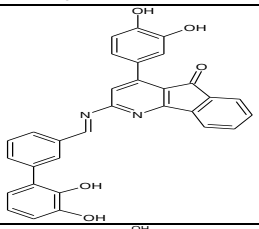
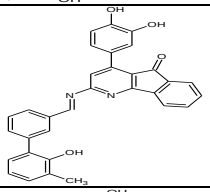
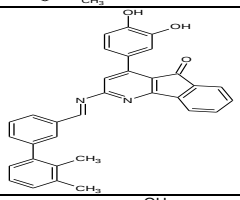
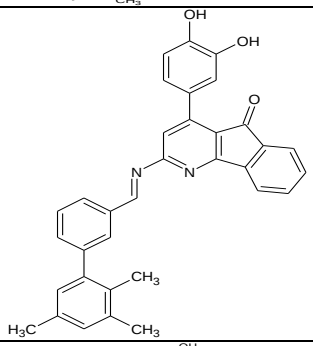
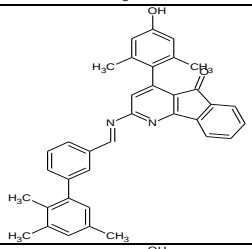
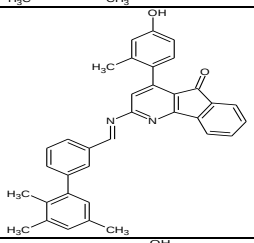
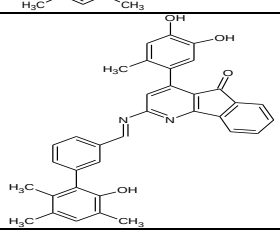
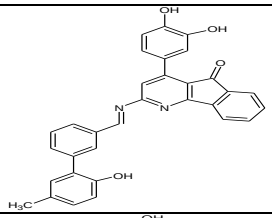
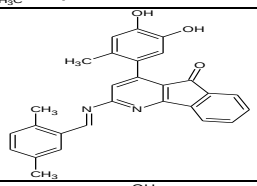
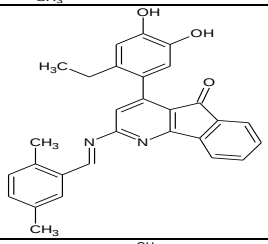
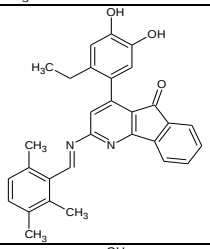
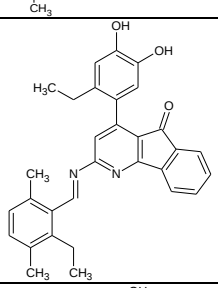
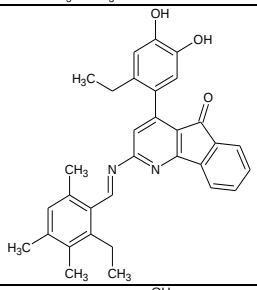
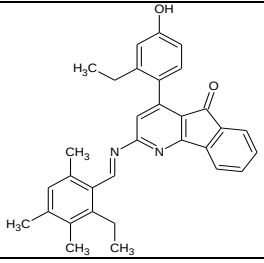
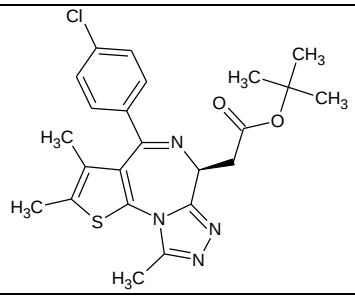
Compound Code	Compound structure	Ames Mutagenicity	Rat oral LD_{50}	Skin irritation	Ocular irritation
2a		6.06	0.55	None	Mild
2b		2.35	1.53	None	Mild
2c		2.90	1.04	None	Mild

Table No. 3b: Toxicity Studies:

Compound Code	Compound structure	Ames Mutagenicity	Rat oral LD_{50}	Skin irritation	Ocular irritation
2d		4.07	1.01	None	Mild
2f		1.24	1.86	None	Mild
2g		2.38	3.98	None	Mild
2h		1.97	1.67	None	Mild

2i		4.14	3.28	None	Mild
2j		4.21	1.60	None	Mild
2k		3.75	0.84	None	Mild
2l		4.31	0.67	None	Mild
2m		4.21	1.11	None	Mild
2p		3.05	0.55	None	Mild
2q		2.53	0.89	None	Mild
2r		3.37	0.68	None	Mild

2s		4.63	2.25	None	Mild
2t		1.62	0.94	None	Mild
2u		1.32	0.72	None	Mild
2v		2.10	0.32	None	Mild
2w		1.52	0.29	None	Mild
2x		1.24	0.40	None	Mild
2y		0.97	0.53	None	Mild

Compound Code	Compound structure	Ames Mutagenicity	Rat oral LD_{50}	Skin irritation	Ocular irritation
JQ1		-16.80	0.26	None	Mild

3.4. DOCKING STUDIES:

Accelrys drug discovery studio 3.5. was carried out for methoxy substituted pyrimidine derivatives compound and standard compound JQ1 inhibitor for bromodomain receptor using Accelrys drug discovery studio 3.5 with PDB Code **4HY3**. It was found that compounds **2c, 2f, 2h, 2i, 2j, 2k, 2l, 2m, and 2s** showed good CDOCKER interaction energy ranges from **-29.80 to -25.06 kcal/mole**. Among them, compound **2c** possesses good CDOCKER interaction energy with the bromodomain receptor, and hence it is expected to bind with the receptor more effectively than other compounds. Whereas the standard compound doesn't possess any interaction with any of the amino acids. Thus, as compared to the standard compound. Compound **2c** interact with ARG 16 having hydrogen bond distance **2.30 Å** while other compounds 2f, 2h, 2i, 2j, 2k, 2l, 2m, and 2s interact with **ARG 16, SER 83 and ILE 21.** Shows better anti-cancer activity are shown in **Table 4** Docking study indicated that the compound 2c binds with important amino acid residues present in the receptor. Hence we hypothesized that the designed pyrimidine derivatives can be an inhibitor of bromodomain.

Table No. 4: DOCKING RESULTS WITH 4HY3

Compound Code	(-) C Docker_Interaction_Energy	Interaction Ligand_Residue	H-bond distance in Å	Interacting amino acids
JQ1	28.97	-	-	-
2a	25.26	-	-	-
2b	24.52	-	-	-
2c	29.80	Attached to OH	2.30	ARG 16
2d	23.32	-	-	-
2f	26.42	Attached to OH Attached to OH	2.05 2.57	ARG 16 SER 83
2g	25.61	-	-	-
2h	25.69	Attached to OH	2.85	ARG 16
2i	25.06	Attached to OH	1.92	ARG 16
2j	27.73	Attached to OH	2.45	ARG 16
2k	28.40	Attached to OH Attached to OH	1.89 1.99	ILE 21 ARG 16
2l	28.49	Attached to OH	2.53	ARG 16
2m	28.92	Attached to NH	2.11	ILE 21
2p	25.77	-	-	-
2q	26.22	-	-	-
2r	25.03	-	-	-
2s	29.02	Attached to OH	1.83	ARG 16
2t	25.78	-	-	-
2u	24.61	-	-	-

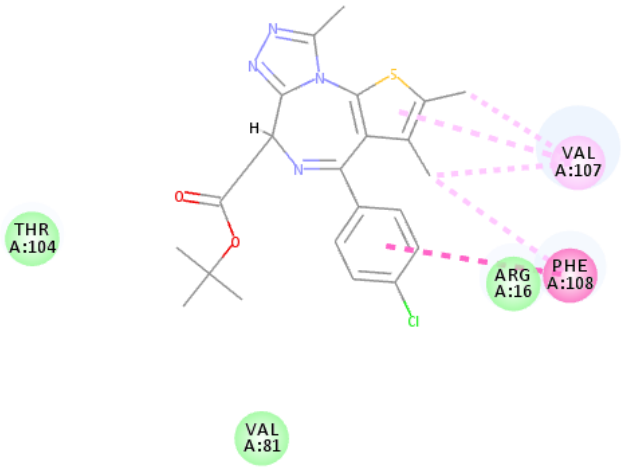


Figure No. 1: Binding interaction between JQ1 with BRD4

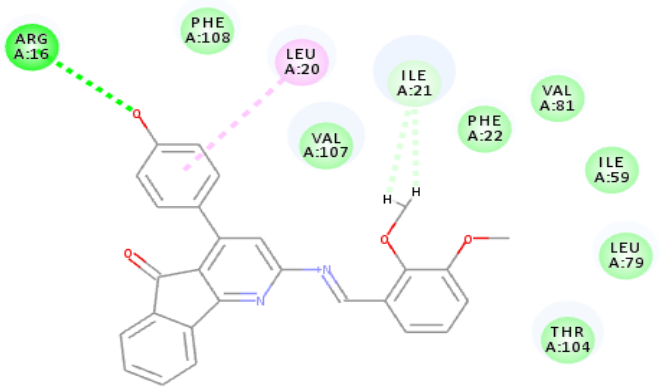


Figure No. 2: Binding interactions between 2C with BRD4

4. CONCLUSION

In this *In silico* study, the series of novel pyrimidine derivatives compound were designed bearing methoxy substituted. All the designed compounds were loaded into Accelrys drug discovery Studio 3.5. to understand the characteristic properties of novel molecule with their drug likeness, ADME, virtual toxicity studies. From the above *in silico* studies, it was concluded that the compound **2c** possesses good CDOCKER interaction energy, good hydrogen bonding distance **2.30Å** and interacts with different amino acid where as the standard compound does not have hence, we hypothesized that the designed pyrimidine derivatives can be an inhibitor of BRD 4.

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6. REFERENCES

1. Panno J. Cancer, Role of Genes, Lifestyle, and Environment. The new biology. 2005:1-177.
2. Prachayasittikul S, Worachartcheewan A, Nantasenamat C. European Journal of Medicinal Chemistry Synthesis and structure e activity relationship of 2-thiopyrimidine-4-one analogs as antimicrobial and anticancer agents. Eur J Med Chem [Internet]. 2011;46(2):738–42. Available from: http://dx.doi.org/10.1016/j.ejmech.2010.12.009.
3. Prachayasittikul S, Pingaew R, Worachartcheewan A, Sinthupoom N, Prachayasittikul V, Ruchirawat S, et al. Roles of Pyridine and Pyrimidine Derivatives as Privileged Scaffolds in Anticancer Agents. Bentham Sci. 2017;869–901.
4. Dhalluin C, Carlson JE, Zeng L, He C, Aggarwal AK, Zhou M. Structure and ligand of a histone acetyltransferase bromodomain is similar to that of acetyl-CoA by histone acetyl. Nature. 1999;399:491–6.
5. Rousseaux S, Steuerwald U, Curtet S, Morinie J, Gaucher J, Sadoul K, et al. Cooperative binding of two acetylation marks on a histone tail by a single bromodomain. Nature. 2009;461:1-6.
6. Dey A, Chitsaz F, Abbasi A, Misteli T, Ozato K. The double bromodomain protein Brd4 binds to acetylated chromatin during interphase and mitosis. PNAS. 2003;100:1-6.
7. Filippakopoulos P, Picaud S, Mangos M, Keates T, Lambert J, Barsyte-lovejoy D, et al. Resource Histone Recognition and Large-Scale Structural Analysis of the Human Bromodomain Family. Cell. 2012;149:214–231.
8. Jang MK, Mochizuki K, Zhou M, Jeong H, Brady JN, Ozato K. The Bromodomain Protein Brd4 Is a Positive Regulatory Component of P-TEFb and Stimulates RNA Polymerase II-Dependent Transcription. Mol Cell. 2005;19:523–34.
9. Yang Z, Yik JHN, Chen R, He N, Jang MK, Ozato K, et al. Recruitment of P-TEFb for Stimulation of Transcriptional Elongation by the Bromodomain Protein Brd4. Mol Cell. 2005;19:535–45.
10. Shi J, Wang Y, Zeng L, Wu Y, Deng J, Zhang Q, et al. Article Disrupting the Interaction of BRD4 with Diacetylated Twist Suppresses Tumorigenesis in Basal-like Breast Cancer. Cancer Cell [Internet].2014;25(2):210–25. Available from: http://dx.doi.org/10.1016/j.ccr.2014.01.028
11. Zou Z, Huang B, Wu X, Zhang H, Qi J, Bradner J, et al. Brd4 maintains constitutively active NF- k B in cancer cells by binding to acetylated RelA. Nature. 2013;1–10.
12. Jayne H, Stewart S, Horne GA, Bastow S, James T, Chevassut T. Cancer Med. 2013;1-10.
13. Schweiger M, Ottinger M, You J, Howley PM, Schweiger M, Ottinger M, et al. Brd4-Independent Transcriptional Repression Function of the Papillomavirus E2 Proteins Brd4-Independent Transcriptional Repression Function of the Papillomavirus E2 Proteins. J. Virol. 2007; 81(18):1-12.
14. Prinjha R, Tarakhovsky A. Chromatin targeting drugs in cancer and immunity. 2013;1731–8.
15. Bayarsaihan D. Epigenetic Mechanisms in Inflammation. J Dent Res. 2011;90:1-10.
16. Giles D. Pyrimidine Derivatives as Dual Inhibitors of COX-2 and STAT-3 as Potential Anticancer and Pyrimidine Derivatives as Dual Inhibitors of COX-2 and STAT-3 as Potential Anticancer and Anti-Inflammatory Agents – An In Silico Approach. IJPPS. 2015;0–25.