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Pyrimidine Derivatives as Dual Inhibitors of COX-2 and STAT-3 as Potential Anticancer and Anti-Inflammatory Agents – An *In Silico* Approach

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ABSTRACT

Several pyrimidine derivatives were designed for its dual targeted inhibition towards COX-2 and STAT-3. Molecular docking was performed for 28 designed ligands against its dual inhibition towards COX-2 and STAT-3 receptors. The results revealed the type of interactions present between the receptors and ligands for standard and the designed compounds. Some of the designed compounds possess good binding affinity towards COX-2 and STAT-3. Among all designed compound **A28** was found to possess good CDOCKER interaction energy, ADME parameters, and Lipinski Rule of 5. These derivatives could be an effective lead in the discovery of dual targeted molecules for the treatment of breast cancer.

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INTRODUCTION

Breast cancer is the second most common type of cancer after lung cancer and the fifth most common cause of cancer death[1]. The design of drugs is thus a major challenge for the medicinal chemists as well as the pharmaceutical companies. Tumor growth and metastasis can be promoted by proinflammatory cytokines by the alteration in tumor cell biology and the activation of stromal cells in the tumor microenvironment. Systemic inflammation may also promote extravastation and growth of reactive dormant tumors at distant sites. Inflammation and breast cancer can be linked in such a way that there is an elevated chance of recurrence in case of cancer survivors who has chronic inflammation because of the inflammatory processes on cell growth or due to the presence of cancer cells that induce inflammation[2]. Inflammation is an enabling characteristic feature of malignant growth. The intensive relationship between tumor and its microenvironment reveals the presence of inflammation, immunologic response, angiogenesis and fibrinogenesis. Inflammation is stimulated by the genetic alterations which will ultimately result in tumor promoting microenvironment. COX-2, cytokines, chemokines and prostaglandins are the major mediators relating inflammation and cancer[3]. Overexpression of COX-2 can be seen in 40% of invasive breast cancer and is associated with increased proliferation, metastasis and reduced survival. Among the seven STAT family members, STAT-3 has a close relation with tumorigenesis[5]. Initially STAT-3 is located in the cytoplasm in their inactive form, and on stimulation by extracellular signals such as cytokines and hormones, activation of Janus Kinases occur and it will phosphorylate STAT-3 at tyrosine residue 705 which will dimerize through their Src-homology 2 domains, which will translocate to the nucleus thereby regulating the expression of various genes involved in cell cycle progression, proliferation, migration, invasion and survival[6]. Abnormal STAT-3 activation has been found in the development of a variety of solid and hematological tumors such as leukemia, lymphomas, head and neck cancers[7].

Most of the anticancer drugs are monotargeted towards cancer. Use of dual targeting strategies and applying pharmacophore group of different active compounds could be useful for the design of most successful drugs. Pyrimidine is being considered as one of the most active anti-inflammatory[8-10] and anticancer[10-12] compound because of its target specificity. Triazole[13-15] and sulphonamide[16-18] derivatives are also found to possess good anti-inflammatory and anticancer

activity. Considering it in mind, it was envisioned to design pyrimdine derivatives containing pharmacophore of triazole and sulphonamides for its dual inhibition towards COX-2 and STAT-3 by *in silico* tools for its anticancer and anti-inflammatory activity.

2. MATERIALS AND METHODS

A typical docking study requires three computational steps before running the docking program: (1) preparation of the receptor, (2) preparation of the ligand, and (3) setup of the parameters of the docking program(s).

The following subsections describe these three steps in detail.

2.1. Receptor preparation

The three dimensional structure of STAT-3 (PDB CODE-1BG1) and COX-2 (PDB CODE-1CX2) were 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 (proteins and DNA) and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy[19].

2.2. STAT-3

The structure contains residues 136 to 716 of STAT-3, half a DNA duplex and 127 water molecules per asymmetric unit. For preparing the receptor, the residues 586 to 688 were selected from the SH2 domain. The water molecules and the DNA duplex were ignored. Hydrogen was added and the receptor was subsequently prepared from prepare protein tools using Discovery Studio 3.5.

2.3. COX-2

COX-2 protein was prepared by retaining only A chain and its crystal ligand. The water molecules and heteroatoms were deleted. Then hydrogen atoms were added and by keeping fixed atom constraints on side chain and backbone of the receptor molecule, only the hydrogen's were minimized.

2.4. Ligand preparation

Structures of the compounds were drawn by using Chemsketch and then the ligands were loaded in Discovery Studio 3.5. It was also used to predict the properties of ligands such as molecular weight, logP value, surface area, number of hydrogen bond donors and acceptors. The 2D structures were subjected to absorption, distribution, metabolism, excretion and toxicity (ADMET) analyses for solubility, intestinal absorption, hepatotoxicity, plasma protein binding ability, blood-brain barrier (BBB) penetration, cytochrome P450 inhibition, and AMES mutagenicity using Discovery Studio 3.5.

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.

2.5. DRUG LIKENESS EVALUATION

Discovery Studio 3.5 was used to predict the drug likeness property of the compounds with the help of Lipinski drug filter. By means of this prediction of Lipinski rule of 5 for the compounds based on its 2D structure can be done and thus provides information regarding the utilization of compounds as a commercial drug[20].

2.6. ADMET DESCRIPTORS

Absorption, Distribution, Metabolism and Excretion (ADME) studies is a good tool to know much about the pharmacokinetic property of the compounds. Aqueous solubility, Blood brain barrier level, CYP2D6, Hepatotoxicity and Plasma Protein Binding level were studied[21].

2.7. MOLECULAR SIMULATION STUDIES

Both protein minimization and ligand minimization were done using CHARMM force field in Discovery Studio 3.5 which is a highly flexible molecular mechanics and dynamics program, having its origin from the program CHARMM (Chemistry at HARvard Molecular Mechanics). CHARMM performs well over a broad range of calculations and simulations, including calculation of geometries, interaction and conformation energies, local minima, barriers to rotation, time-dependent dynamic behavior, and free energy[22].

2.8. TARGET PROTEIN AND ACTIVE SITE PREDICTION

The most important or favoured regions of the proteins were evaluated by means of various literature survey and the site was selected with the presence of most active amino acids within different active sites of protein.

2.9. MOLECULAR DOCKING

Docking was mainly carried out by using Discovery Studio 3.5. The required structure of proteins and ligands were prepared. The prepared proteins were defined as receptor molecule by clicking on define selected molecule as receptor under define and edit binding site and by selecting only the ligand part and clicking on define sphere from receptor site. By means of this the crystal ligand defined the binding site of 9Å on the receptor molecule. Now the prepared receptor molecule can be input for input receptor molecule parameter in the CDOCKER protocol parameter explorer. Each of the molecules were given as input in other parameter meant for input ligands and the protocol were run as many times as the number of inhibitors selected.

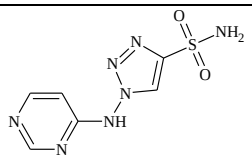
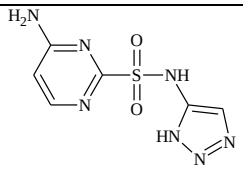
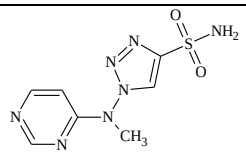
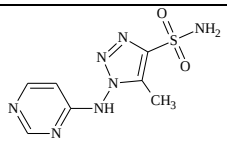
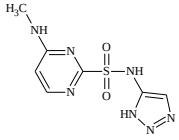
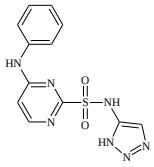
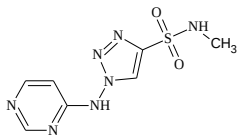
The CDOCKER ENERGY of best poses docked into the receptor of all derivatives was calculated.

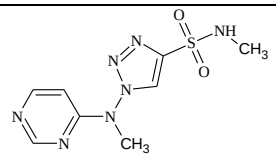
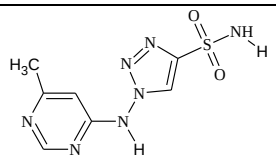
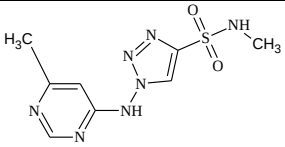
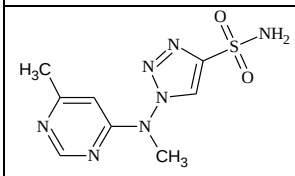
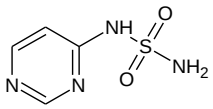
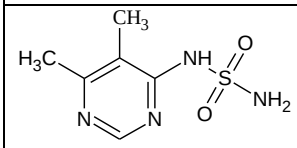
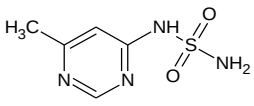
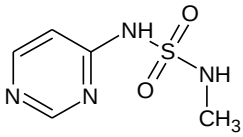
3. RESULTS AND DISCUSSION

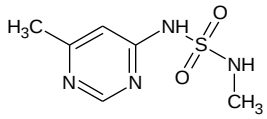
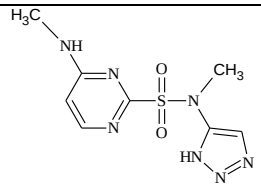
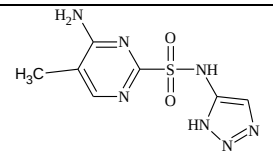
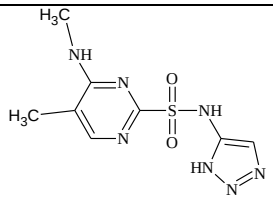
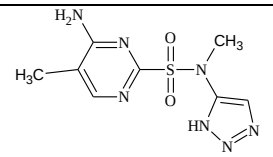
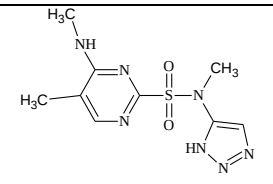
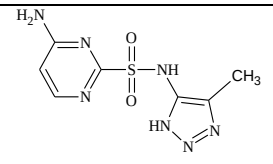
3.1. Drug Likeness:

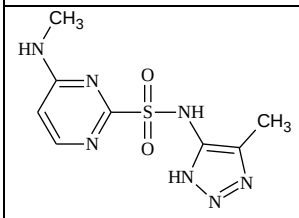
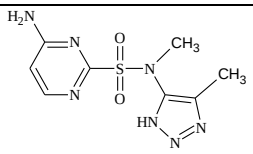
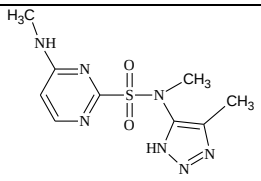
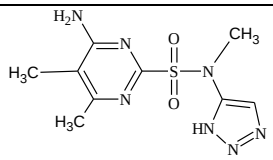
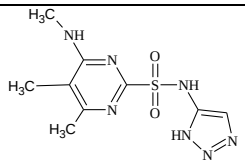
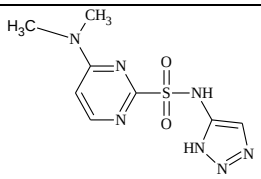
All the designed compounds possessed good number of hydrogen bond donors and acceptor. Most of the designed compounds possess 1 to 4 hydrogen donor and 6 to 9 hydrogen acceptor. The compounds were designed so as to increase the binding of the drug with the receptor mainly by hydrogen bonding. The sulphonamide and triazole moiety was added to increase the binding of the designed molecule with the receptor. All the compounds were found to follow Lipinski rule of 5 since it would increase drug likeness of the designed compounds. The details were specified in **Table 1**. Polar surface area was calculated to optimize the drugs ability to permeate cell membrane. All the designed compounds were within the permissible limit and hence these designed compounds could not possess any problem with bioavailability.

Table 1: Drug likeness

Compounds	Compound code	No. of hydrogen bond donor	No. of hydrogen bond acceptor	A log P	Mol weight	Molecular fractional polar surface area
	A1	3	9	-0.384	241.23	0.642
	A2	4	9	-1.047	241.23	0.686
	A3	2	9	-0.179	255.25	0.547
	A4	3	9	-0.239	255.25	0.591
	A5	3	9	-0.492	255.25	0.581
	A6	3	9	1.25	317.32	0.482
	A7	2	9	-0.179	255.25	0.537

Compounds	Compound code	No. of hydrogen bond donor	No. of hydrogen bond acceptor	A log P	Mol weight	Molecular fractional polar surface area
	A8	1	9	0.027	269.28	0.457
	A9	3	9	-0.102	255.25	0.591
	A10	2	9	0.104	269.28	0.496
	A11	2	9	0.104	269.28	0.506
	A12	3	6	-1.32	174.18	0.659
	A13	2	6	-1.114	188.20	0.522
	A14	3	6	-1.037	188.20	0.591
	A15	2	6	-0.831	202.23	0.472

Compounds	Compound code	No. of hydrogen bond donor	No. of hydrogen bond acceptor	A log P	Mol weight	Molecular fractional polar surface area
	A16	3	9	-0.841	255.25	0.586
	A17	2	9	-0.286	269.28	0.495
	A18	4	9	-0.561	255.25	0.629
	A19	3	9	-0.005	269.28	0.535
	A20	3	9	-0.355	269.28	0.542
	A21	2	9	0.201	283.31	0.462
	A22	4	9	-0.764	255.25	0.631

Compounds	Compound code	No. of hydrogen bond donor	No. of hydrogen bond acceptor	A log P	Mol weight	Molecular fractional polar surface area
	A23	3	9	-0.209	269.28	0.536
	A24	3	9	-0.558	269.28	0.543
	A25	3	9	-0.072	283.31	0.505
	A26	3	9	0.277	283.31	0.497
	A27	4	9	-0.278	269.28	0.583
	A28	2	9	-0.138	269.28	0.495

3.2. ADME INVESTIGATION:

Discovery Studio 3.5 was used to calculate *in silico* ADME parameters. They were calculated to avoid failure of the drug in the final stages of discovery process. All the designed 28 compounds possessed absorption level in the range of 0 and 1 which indicates that the designed compounds

possessed moderate to good absorption. The aqueous solubility level and BBB level were in the range of 3-4 indicating that the designed compounds possessed optimal solubility with undefined BBB level. Inhibition level of CYP2D6 and hepatotoxic level were 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 2: ADME investigation of the designed compounds

Compounds	Absorption level	Aqueous solubility level	BBB level	CYP 2D6	Hepatotoxicity level	PPB level
A1	1	3	4	-8.9880	0.4063	-6.7628
A2	1	4	4	-9.2190	0.0487	-5.2246
A3	0	4	4	-9.0160	0.5051	-5.8688
A4	1	3	4	-9.6614	0.0857	-6.1192
A5	1	4	4	-12.3536	0.4973	-3.6740
A6	0	3	4	-10.8545	0.0081	1.0730
A7	0	4	4	-9.5639	0.5206	-7.0308
A8	0	4	3	-9.4377	0.4608	-5.8238
A9	1	3	4	-9.6050	0.0829	-7.4445
A10	0	3	3	-10.0268	0.0829	-7.3995
A11	0	3	4	-9.7289	0.0706	-6.2375
A12	1	4	4	-7.9731	0.4614	-8.6634
A13	0	4	3	-8.4561	0.3079	-8.4341
A14	0	4	4	-8.1984	0.0043	-8.9271
A15	0	4	3	-7.5827	0.0041	-9.1385
A16	1	4	4	-8.6144	0.0535	-5.8371
A17	0	4	4	-11.4686	0.5294	-4.2359
A18	1	4	4	-13.0490	0.0009	-5.3208
A19	0	3	4	-13.7856	0.0588	-3.1930
A20	1	4	4	-12.1640	0.0011	-6.3051

Compounds	Absorption level	Aqueous solubility level	BBB level	CYP 2D6	Hepatotoxicity level	PPB level
A21	0	3	3	-12.5533	0.0740	-3.0129
A22	1	4	4	-12.3864	0.0107	-3.9782
A23	0	4	4	-13.1229	0.0806	-2.7994
A24	1	3	4	-11.5014	0.0104	-4.9625
A25	1	3	4	-10.9798	0.0083	-5.0215
A26	0	3	4	-12.6014	0.1078	-1.6470
A27	1	3	4	-11.9620	0.0092	-4.9392
A28	0	4	4	-11.9394	0.5200	-2.6707

3.3. VIRTUAL TOXICITY STUDIES

TOPKAT in Discovery Studio 3.5 predicts toxicity endpoints based on chemical structure, including NTP Carcinogenicity Call (Female Rat, Male rat), Ames Mutagenicity, Rat Oral LD50, Skin Irritation, Developmental toxicity. Various models that can be calculated are tabulated in the **Table 3.** Models which satisfy all the validation criteria for the query compound were computed and results were recorded.

Mutagenicity predicts the ability of the drug to cause mutation to human cells and is based on Ames test. Carcinogenicity assay predicts the ability of the compound to cause cancer to normal human cells. Carcinogenicity assay predicts the ability of the compound to cause cancer to normal human cells. Carcinogenicity test are carried for male and female mouse model. Toxicity prediction studies serves as a preclinical examination and helps to minimize the time and cost during clinical trials. Skin irritation test provides information on the use of compound for topical applications. Computed Probability should be used to determine toxicity. If it is between 0 and 0.29, the compound is non-toxic, if it is between 0.3 and 0.69, the result is indeterminate, and if the score is between 0.7 and 1, the compound is toxic. It has been observed that if the discriminant score is negative then probability of causing cancer is 0 or non-carcinogenic, if discriminant score is positive then probability of causing cancer, mutagenicity and

developmental toxicity is 1 or carcinogenic, mutagenic and developmental toxicity exist. For Rat LD50 the model should fall in between the range. Since the discriminant score of all the compounds found to be negative, the compounds were found to be non-carcinogenic.

Table 3: Toxicity Studies

Ligands	NTP Carcinogenicity Call (Female Rat)	Computed probability	NTP Carcinogenicity Call (male Rat)	Computed probability	Ames Mutagenicity	Developmental toxicity	Rat Oral LD50	Skin Irritation	computed probability
A1	-2.095	0.503	-4.189	0.343	-2.438	-2.012	-0.888	0.690	0.974
A2	-2.792	0.469	-4.068	0.355	-4.804	1.276	-0.836	-1.622	0.958
A3	-3.077	0.454	-2.817	0.465	-1.966	-1.787	-0.546	-0.311	0.977
A4	-2.465	0.486	-3.738	0.386	-2.219	-2.929	-0.810	-0.644	0.974
A5	-3.448	0.434	-2.732	0.471	-4.518	-1.868	-0.729	-1.563	0.959
A6	-6.127	0.264	-4.392	0.324	-5.980	-4.826	-1.046	-4.794	0.408
A7	-3.611	0.424	-4.044	0.357	-2.054	-1.654	-1.691	-1.069	0.969
A8	-3.952	0.404	-4.112	0.351	-1.797	-1.222	-0.417	-0.736	0.973
A9	-2.935	0.462	-3.591	0.399	-2.087	-3.103	-2.077	-0.663	0.974
A10	-4.347	0.380	-3.971	0.364	-1.902	-2.589	-2.557	1.088	0.969
A11	-3.813	0.412	-2.743	0.471	-1.814	-2.722	-0.826	-0.330	0.976
A12	-1.858	0.514	-3.341	0.422	-6.918	-0.134	-0.811	-1.152	0.968
A13	-3.023	0.457	-4.204	0.342	-5.420	0.258	-1.578	-1.765	0.954
A14	-3.942	0.405	-3.211	0.433	-6.693	-0.780	-2.391	-1.244	0.966
A15	-4.271	0.385	-3.438	0.413	-5.339	-1.336	-2.999	-1.717	0.955
A16	-2.266	0.495	-6.167	0.161	-2.055	-1.688	-0.209	-1.321	0.964
A17	-3.600	0.425	-4.847	0.280	-2.154	-2.124	-0.081	-1.793	0.953
A18	-3.078	0.454	-3.789	0.381	-5.463	-1.965	1.036	-1.576	0.959
A19	-3.157	0.450	-2.316	0.502	-5.193	-2.078	-0.584	-1.562	0.959
A20	-2.674	0.475	-5.903	0.183	-2.954	-2.221	-0.167	-1.321	0.965

Ligands	NTP Carcinogenicity Call (Female Rat)	Computed probability	NTP Carcinogenicity Call (male Rat)	Computed probability	Ames Mutagenicity	Developmental toxicity	Rat Oral LD50	Skin Irritation	computed probability
A21	-3.082	0.454	-5.447	0.223	-2.827	-2.283	-0.063	-1.861	0.950
A22	-3.828	0.412	-4.085	0.353	-4.190	-2.193	-1.713	-1.497	0.961
A23	-4.606	0.363	-2.297	0.503	-4.102	-2.630	-0.966	-1.483	0.961
A24	-3.424	0.435	-6.199	0.159	-1.681	-2.501	-0.277	-1.242	0.966
A25	-3.702	0.419	-3.531	0.405	-4.478	2.158	-2.466	-1.567	0.959
A26	-2.433	0.487	-5.746	0.196	-2.053	-2.414	-0.388	-1.312	0.965
A27	-3.781	0.414	-2.628	0.479	-4.281	-2.651	-1.351	-1.622	0.958
A28	-4.599	0.364	-2.814	0.465	-6.331	-0.798	-0.263	1.243	0.966

3.4. DOCKING STUDIES:

Docking studies of the designed compounds were carried out to find out the best fit orientation of the molecule with the specified target. The designed compounds were docked into COX-2 and STAT-3. Docking was performed using Discovery Studio 3.5. From the results obtained it was observed that all the designed compounds exhibited good binding with the targets. CDOCKER interaction energy for all the compounds ranges from -35.2648 to -18.9376 with COX-2 receptor and from -245.0965 to -14.0136 with STAT-3 receptor.

Most of the compounds interact with amino acids such as ARG 120, ARG 513, GLU 524, TYR 355, VAL 523 with COX-2. The standard indomethacin binds with ARG 120 with a hydrogen bond distance of 2.1638 Å. Most of the designed compounds were involved in binding with ARG 120. **A28** possesses CDOCKER interaction energy of -19.3651 while the standard possesses CDOCKER interaction energy of -33.3379. The CDOCKER energy of **A28** was found to be 10.7310 Å. Compound **A28** binds with ARG 120 with a hydrogen bonding distance of 2.3088 Å. **A28** also interacts with amino acids ARG 513 and TYR 355 with two hydrogen bonds distance of 1.8412 Å and 2.1253 Å respectively **(Fig: 1)**.

In STAT-3 receptor LEU 607, LEU 670, THR 622, SER 668, TYR 657 and PRO 669 were involved in the binding with the designed derivatives. 5-Flurouracil was found to interact with LEU 670 in which nitrogen of pyrimidine was involved in binding with a hydrogen bonding distance of 2.4274 Å. Derivative **A1**, **A2**, **A4**, **A6**, **A7**, **A8**, **A9**, **A12**, **A20**, **A22**, **A23**, **A24**, **A26**, **A27** and **A28** were found to involve in binding with LEU 670. **A28** possesses good CDOCKER interaction energy of -245.0965 while the standard possesses CDOCKER interaction energy of -14.0136. The CDOCKER energy of **A28** was found to be 606.7724. Hence the designed compound **A28** was expected to have good binding with STAT-3. A28 found to bind with LEU 670 with a hydrogen bonding distance of 2.2633 Å. **A28** also binds with ILE 654 with a hydrogen bonding of 1.8080 Å **(Fig: 2)**. Among all the designed compounds, **A28** binds with COX-2 and STAT-3 effectively and hence it could act as a dual inhibitor for the treatment of cancer related inflammation.

Table 3: DOCKING RESULTS WITH COX-2

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
Indomethacin	4.7584	-33.3379	Double bonded oxygen	2.1638	ARG 120
A1	4.6472	-27.8739	H of NH attached to sulphur	1.9656 2.1681	GLU 524
			N of NH attached to sulphur	2.3611	ARG 120
			Double bonded oxygen of sulphonamide	1.7940	ARG 513
				2.0813	ARG 120
			N of triazole	1.9107 2.2897	TYR 355
				2.1128 1.7940	ARG 513
A2	3.1226	-21.8050	N of pyrimidine	2.4694 1.9430	ARG 513 TYR 355

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
			O of sulphonamide	2.4118	TYR 355
			NH of triazole	2.4888	TYR 355
			N of triazole	2.3591	ARG 120
A3	4.5840	-29.5972	N of triazole	1.9777 2.1199	TYR 355
				2.2864	ARG 513
			O of sulphonamide	1.7170	ARG 513
			N attached to sulphonamide	2.3519	ARG 120
			H of NH	2.2560 1.9112	GLU 524
A4	8.7015	-23.8511	H of NH	2.2474 1.9618	GLU 524
			O of Sulphonamide	1.9711	ARG 513
			N of triazole	2.1801 2.3236	ARG 513
			N of Sulphonamide	1.8280 2.2241 2.4361	TYR 355
			O of Sulphonamide	2.0544	ARG 120
A5	9.1760	-24.3321	O of Sulphonamide	2.3324	ARG 120
			N attached to sulphonamide	2.1326	TYR 355
A6	3.1207	-32.4412	N of triazole	2.4660 2.4708	ARG 513

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
A7	9.3646	-25.9145	N of Pyrimidine	2.3464 2.2021	ARG 513 TYR 355
			N of triazole	2.4567	ARG 120
A8	4.6487	-30.0097	O of Sulphonamide near to NH	2.3626	ARG 120
			N of Triazole	2.2462 1.9128	TYR 355
			O of Sulphonamides	2.4404	ARG 513
			H of NH	1.8208 1.8670	GLU 524
A9	-	-			
A10	7.2494	-26.6509	O of Sulphonamide	2.1807	ARG 120
			N of Pyrimidine	2.2308	ARG 513 TYR 355
			N of Triazole	2.1846	TYR 355
A11	3.5591	-27.0402	H of NH attached to sulphonamides	2.0131	TYR 355
			N of Triazole	1.8966 2.4472	TYR 355
			O of Sulphonamides	2.0794 1.9840	ARG 513
A12	22.8870	-19.1282	O of Sulphonamides	2.3236	ARG 120
			O of Sulphonamides near to NH	1.7234	ARG 513

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
			H of NH attached to sulphonamides	2.3639 2.0949	VAL 523 GLU 524
A13	24.7808	-26.2320	O of Sulphonamides near to NH	2.4271	ARG 120
			N of Pyrimidine	2.1615	TYR 355
			O of Sulphonamides	1.8589 2.2805	ARG 513
			H of NH attached to sulphonamides	1.8815	GLU 524
A14	27.9044	-23.5509	O of Sulphonamides near to NH	2.3072	ARG 120
			N of Pyrimidine	1.9520	TYR 355
			O of Sulphonamides	2.2790 2.2932	ARG 513
			H of NH attached to sulphonamides	2.0149	GLU 524
A15	27.9909	-25.2366	H of NH attached to sulphonamides	1.9897	TYR 355
			O of Sulphonamides near to NH	2.0033 1.8993	
A16	13.5966	-21.3381	N of Pyrimidine	1.9127	TYR 355
			H of NH attached to pyrimidine	2.1358	GLU 524

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
A17	7.8534	-27.6554	N of Pyrimidine	1.9389	TYR 35
			O of Sulphonamides	2.3334	
A18	0.5896	-27.3886	O of Sulphonamides	2.3136	TYR 355
			N of Triazole	2.4273	ARG 513
A19	10.0287	-26.2053	O of Sulphonamides	2.3305	ARG 120
			Attached to Nitrogen	2.0907	TYR 355
A20	11.8263	-25.8145	O of Sulphonamides	2.4661	TYR355
			N of Pyrimidine	1.8928	ARG 513
			N of Pyrimidine	2.4107	ARG 513
			H of NH attached to Pyrimidine	2.2294	GLU 524
A21	9.1907	-29.4097	O of Sulphonamides	2.1656	ARG 120
A22	4.4912	-20.0767	N bonded to both Sulphonamides and Triazole	1.9942	TYR 355
A23	2.2692	-25.1532	N of Pyrimidine	1.9144	TYR 355
A24	15.6681	-18.9376	N of Pyrimidine	1.9095	TYR 355
			H of NH attached to Pyrimidine	2.1913	GLU 524

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
A25	3.1220	-26.4823	O of Sulphonamides	2.2640	ARG 120
			N bonded to both Sulphonamides and Triazole	2.1612	TYR 355
A26	14.2758	-23.5722	N of Pyrimidine	1.9528	TYR 355
			O of Sulphonamides	2.4218	
			H of NH attached to Pyrimidine	2.2364	GLU 524
A27	4.7963	-35.2648	O of Sulphonamides	2.3586	TYR 355
			N of Triazole	2.4300	ARG 120
A28	10.7310	-19.3651	N bonded to both Sulphonamides and Triazole	1.8412	ARG 513
			O of Sulphonamides	2.3088	ARG 120
			N of Pyrimidine	2.1253	TYR 355

Table 4: Docking results with STAT-3

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
5-Flouro uracil	14.5038	-14.0136	N of pyrimidine Attached to OH	2.4274 2.0676 2.1532	LEU 670
A1	272.3031	-95.8681	N of triazole	1.8215	LEU 670
			NH attached to triazole	1.9367	
A2	324.1221	-100.1162	NH attached to pyrimidine	1.8700	SER 668
			N of pyrimidine	2.3371	LEU 670
A3	765.3420	-162.4771	NH of Sulphonamides	2.1379	THR 622
A4	479.0082	-154.7894	N of pyrimidine	1.9653	LEU 670
			NH_2 of Sulphonamides	1.7725 1.8941	LEU 607
A5	262.7982	-114.1830	N of Triazole	2.3945	THR 622
A6	591.7151	-162.7320	O of Sulphonamides	2.1264	THR 622
			N of Triazole	1.8126 2.0703	LEU 670
A7	942.3981	-160.1220	N of Triazole	2.3546	LEU 670
			N attached to pyrimidines and triazoles	1.9743	LEU 670
A8	636.8281	-160.2950	O of Sulphonamides	2.4952	LEU 670
A9	299.0880	-118.4520	NH of triazole	1.4371	LEU 670
			NH attached to triazole and pyrimidine	2.0622	

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
A10	518.2831	-155.5770	N of Pyrimidines	2.3592	SER 668
A11	551.1960	-162.7411	N of Pyrimidines	2.3592	SER 668
A12	37.5491	-20.0733	N of Pyrimidines	2.2893	LEU 670
			NH_2 of sulphonamides	2.3897 2.2468	
A13	61.2560	-28.3578	N attached to sulphonamides and pyrimidine	2.1187	THR 622
A14	75.2294	-40.8447	N attached to sulphonamides and pyrimidine	1.8971	THR 622
A15	142.9130	-72.4240	O of sulphonamides	2.1698	LEU 650
A16	591.7151	-162.7321	O of sulphonamides	2.2748	THR 622
A17	643.5622	-159.7965	N of pyrimidine	2.0921	THR 622
A18	320.4221	-112.9510	O of sulphonamides	2.4531	THR 622
A19	746.5913	-197.9431	N of triazole	1.8691	TRP 623
A20	410.8791	-151.7721	NH attached to pyrimidine	2.4901	LEU 670
A21	598.9551	-211.1753	N of pyrimidine	2.2797	THR 622
A22	263.3132	-128.7871	N of triazole	2.2693	LEU 670
A23	784.9241	-244.7831	NH attached to pyrimidine O of Sulphonamides	2.0139 1.9997	LEU 670

Ligand code	CDOCKER Energy	CDOCKER interaction Energy	Interactions Ligand-Residue	H-bond distance in Å	Interacting amino acids
			NH of triazole	1.8521	THR 622
A24	799.1793	-153.6713	N of pyrimidine	2.1174	LEU 670
			O of sulphonamide	2.1103	
A25	686.8114	-197.7461	N of triazole	1.5600	TRP 623
			N of triazole	2.4925	TYR 657
			N of Pyrimidine	2.4447	LEU 670
			H of Nitrogen of triazole	2.1215	TYR 657
A26	864.7161	-229.3710	N attached to Pyrimidine	2.4923	PRO 669
			N attached to Pyrimidine	1.9034	LEU 670
			H attached to N of triazole	1.9573	ILE 653
A27	857.3230	-236.3113	N of Triazole	1.8611	TRP 623
			N of Triazole	2.3403 1.9976	TYR 657
			N of Pyrimidine	2.3452	LEU 670
A28	606.7724	-245.0965	N of Pyrimidine N of Triazole	2.2633 1.8080	LEU 670 ILE 654

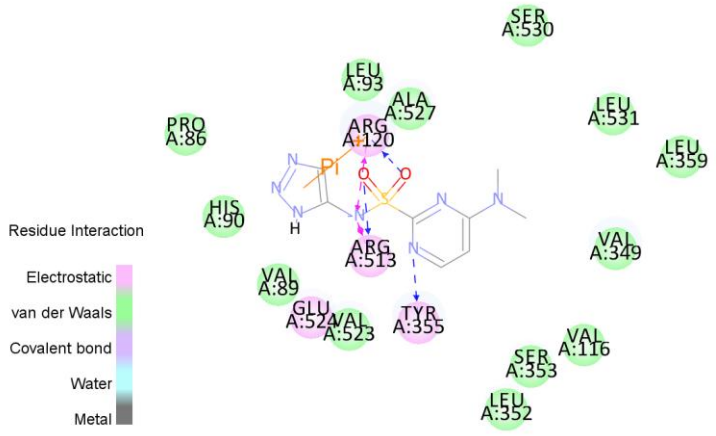


Figure 1: Binding interactions between A28 with COX-2.

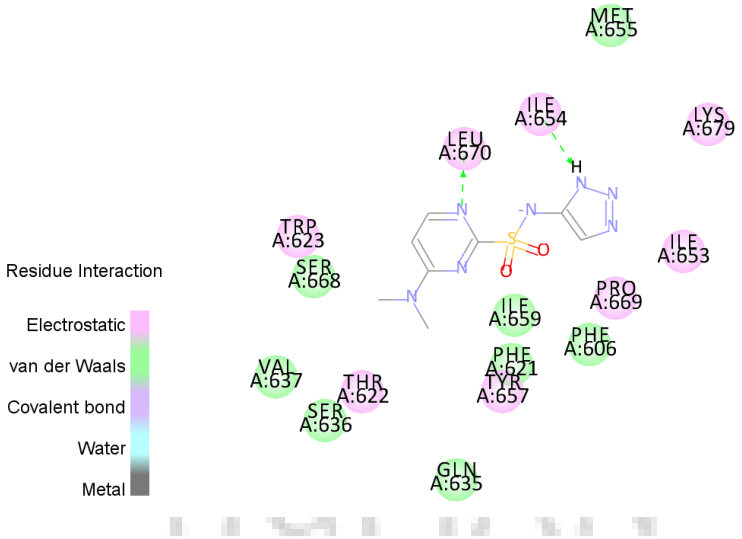


Figure 2: Binding interactions between A28 with STAT-3.

4. CONCLUSION

In the present study 28 pyrimidine derivatives were designed bearing sulphonamide linked with triazole. All the compounds were subjected to drug likeness, ADME, Toxicity sudies and docking. Molecular docking was performed in STAT-3 and COX-2 target using Discovery Studio 3.5. From the above *in silico* studies it was concluded that the compound **A28** possess good characteristics feature for the lead molecule. It possesses good CDOCKER interaction energy and good hydrogen bonding. Presence of pyrimidine linked by sulphonamide to triazole could have caused the molecule to obtain the configuration necessary to bind with the target.

Hence, 4-(dimethylamino)-*N*-(1*H*-1,2,3-triazol-5-yl)pyrimidine-2-sulfonamide (**A28**) could act as lead in the development of compounds targeting cancer related inflammation.

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6. REFERENCES

1.Alex M, Nixon R.Docking Studies on Anticancer Drugs for BreastCancer using Hex.IMECS.2009; 1:18-20.
2.Brandon L, Rachel B, Leslie B, Richard N, Marian L.Elevated Biomarkers of Inflammationare associated with reduced survival among Breast Cancer Patients.JClinOncol.2009; 27(21):3437-43.
3.Maja S, Ana K, LadaB, TamaraA. Protumor effects of proinflammatory mediators in breast cancer.PeriodBiol.2012; 114(4): 489-96.
4.Zhe H, Domenick F, Kotha S, Andrew J. Macrophages induce COX-2 expression in breast cancer cells: role of IL-1β autoamplification. Carcinogenesis.2011; 32(5):695–702.
5.Bhuvanesh D, Melissa D , Lacey E, Meng-Fen W, Xiaomei Z.Selective Small Molecule STAT-3 Inhibitor Reduces Breast Cancer Tumor-Initiating Cells and Improves Recurrence Free Survival in a Human-XenograftModel.Plos One.2012; 7(8):e30207.
6.Liu L, Leung K, Chan D, Wang Y, Ma D, Leung C.Identification of a natural product-like STAT3dimerization inhibitor by structure-based virtualscreening.Cell Death Dis. 2014; 5: e1293.
7. Khandaker A, Zaid S, James T.STAT3 as a target for inducing apoptosis in solid and hematological tumors.Cell Res. 2008; 18(2):254-67.
8.Nofal Z, Fahmy H, Zarea E, El-Eraky W.Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities.Acta Pol Pharm. 2011; 68(4):507-17.
9. Sondhi S, Singh N, Johar M, Kumar A.Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives.Bioorg Med Chem. 2005; 13(22):6158-66.
10.Vachala S, Divya J, Jessy E.Synthesis and biological evaluation of novel pyrimidine-2(1*H*)-ones/thiones as potent anti-inflammatory and anticancer agents.Med Chem Res.2012; 21(11):3598-606.
11.Salman A, Tamara S, Farooq I.Synthesis, Characterization and Cytotoxic Activity of Some Pyrimidine Derivatives.J Al-Nahrain Univ.2013; 16(2):84-92.
12. Manal M, Lamia W, Mohammed K, Ahmed T. Design, Synthesis, and Antitumor Evaluation of Novel Pyrazolo [3,4-*d*] pyrimidine Derivatives.Sci Pharm. 2012; 80: 531-45.
13.Ma L, Pang L, Wang B, Zhang M, Hu B, Xue D et al.,Design and synthesis of novel 1,2,3-triazole-pyrimidine hybrids as potential anticancer agents.Eur J Med Chem. 2014; 86:368-80.
14.Chetan M, Irfan A, Ramesh B, Ramu G.Novel pyrimidine and its triazole fused derivatives: Synthesis and investigation of antioxidant and anti-inflammatory activity.Arabian J Chem. 2014; 7: 986-93.
15.Nitin M, Jyoti A , Dheeraj A , Pankaj M, Tanaji M,Sivakumar T.Synthesis, Antimicrobial and Anti-inflammatory Activity of Some 5-Substituted-3-pyridine-1, 2, 4- Triazoles.Int J PharmTech Res.2010;2(4):2450-55.
16.Keche A, Hatnapure G, Tale R, Rodge A, Birajdar S, Kamble V.A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: synthesis, anti-inflammatory and antimicrobial evaluation.Bioorg Med Chem Lett. 2012;22(10):3445-8.
17. Jainey P, Ishwar B.Microwave assisted synthesis of novel pyrimidines bearing benzene sulfonamides and evaluation of anticancer and antioxidant activities. Asian J Pharm Clin Res.2014; 7(1):111-14.

18.El-Sayed N, El-Bendary E, El-Ashry S, El-Kerdawy M.Synthesis and antitumor activity of new sulfonamide derivatives of thiadiazolo [3, 2-a] pyrimidines.Eur J Med Chem. 2011; 46(9):3714-20.
19.Jie Z,YuanyuanS, XiaoyanP, ChenW, Wenfang X.Molecular Docking, 3D-QSAR Studies, and *In Silico*ADME Prediction of *p*-Aminosalicylic Acid Derivatives as NeuraminidaseInhibitors.Chem Biol Drug Des.2011; 78(4):709-17.
20.Usha T, Middha S, Goyal A, Karthik M, Manoj D, Faizan S et al ., Molecular docking studies of anti-cancerous candidates in Hippophaerhamnoides and Hippophaesalicifolia.JBiomed Res.2014; 28(5):406-15.
21. RichardL, JayarajV, Ranjani, K, Manigandan,NamasivayamE.*In silico* Docking Studies to Identify Potent Inhibitors of Alpha-Synuclein Aggregation in Parkinson Disease.2013; 6(4): 127-131.
22. Pavan K, VivekC, Richard L,Jayaraj, Jagatheesh K, Elangovan N.Chalcones as effective Antimicrobials –a comparative *in silico* approach. Int J Chem Pharm Sci. 2012; 3 (4):67-74.