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RESEARCH ARTICLE

Virtual Screening of Novel Hybrid Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Exploring Multiple Targeted Cancer Therapy by an *In Silico* Approach

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Abstract: ***Background*:** Dual-targeting/Multi-targeting of oncoproteins by a single drug molecule represents an efficient, logical and alternative approach to drug combinations. *In silico* methods are useful tool for the search and design of selective multi-target agents.

***Objective*:** The objective of the present study was to design new hybrid compounds by linking the main structural unit of the NSAIDs with the benzothiazole and thiadiazole ring and to discover new hybrid NSAIDs as multi targeted anticancer agents through *in silico* approach.

***Method*:** Structure-based virtual screening was performed by applying ADMET filtration and Glide docking using Virtual screening Workflow. The docking studies were performed on three different types of receptors TNF-α, COX-II and protein kinase. Bioactivity prediction of screened compounds were done using Molinspiration online software tool.

***Results*:** Out of the 54 designed compounds eighteen were screened on the basis of binding affinity on various receptors and ADMET filtration. Bioactivity prediction reveals that screened compounds may act through kinase inhibition or enzyme inhibition. Compounds 2sa, 5sa, 6sa and 7sa showed higher binding affinity with all three receptors.

***Conclusion*:** The study concluded that compound 2sa, 5sa, 6sa, and 7sa could be further explored for multiple targeted cancer therapy.

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1. INTRODUCTION

Cancer is a major human health issue in the world. The discovery of new target based therapy opened a new window for the treatment of cancer. Major problems in the current cancer chemotherapy are the development of resistance and severe toxic effects. Resistance may occur through several different cellular mechanisms. Therefore, the challenge is to identify new less toxic drug and to improve existing cancer therapy. Active research going on to identify targets whose expression or activation increases cancer growth. Since the last century, there have been major developments in our understanding of cancer at the molecular level [1]. Various growth factors, hormones, cytokines, oncogenes, viruses, bacteria, and carcinogens have been identified that initiate and promote cancer. Many sub-cellular mechanisms promote the growth of cancer cells. Many biomarkers of cancer like hypoxia inducible factor (HIF), CYP450, TNF-α, COX-II, protein kinase, *etc.* have been discovered whose overexpression/dysfunction causes cancer [2-8].

It is well admitted that the link between chronic inflammation and cancer involves cytokines and mediators of inflammatory pathways, which activate several cell survival pathways, which escape the death of tumor cells. The most well known is the case of TNF-*α,* produced by tumor and immune cells, which leads to the survival of cancer cells. [9-11]. TNF-*α* function can be inhibited in two stages: **1**) inhibition of TNF-*α* converting enzyme (TACE), which inhibits Pro TNF-*α* processing. **2**) Inhibition of nuclear factor (NF)-*κB* which inhibits pro TNF-*α* synthesis. TACE inhibitors have been investigated as a means to prevent/limit inflammation by blocking the release of TNF in inflammatory diseases. TMI-005 and BMS-561392 were tested in Phase-II clinical trial but they were unsuccessful due to systemic toxicity and lower efficacy. Toxicities observed due to the inhibition of MMPs, including MMP1, MMP2, and MMP13. Therefore, there is a need to develop specific TACE inhibitors which are non specific target for MMPs to reduce toxicities. Currently, specific TACE inhibitors have shown great

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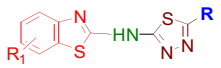
Table 1. Designed hybrid pharmacophores.



R		R1	
Compound name	**Code**	**Substitution**	**Code**
Salicylic acid	sa	7-CH_3	1
Aspirin	a	5-CH_3	2
Ibuprofen	ib	7-NO_2	3
Naproxen	na	5-NO_2	4
Fenoprofen	fp	7-OCH_3	5
Ketoprofen	kp	5- OCH_3	6
-		5-Cl	7
		7-Cl	8
		H	9

promising results in anti-inflammatory preclinical studies and are under investigation. These trials highlight the potentials and the challenges associated with the use of TACE inhibitors in treating breast cancer patients [12].

Over-expression of COX-II has been detected in a number of different types of cancer such as colorectal, breast, pancreatic and lung cancers which escape apoptosis due to elevated PGE_2 levels [13-15]. The chemopreventive effect of non steroidal anti-inflammatory drugs (NSAIDs) in colon and several other cancers is modern approach for cancer therapy [16]. It may also be implicated in tumor promotion, where inflammation triggers the secretion of growth factors, such as the epithelial (EGF) and fibroblast growth factors (FGF) [17].

Protein kinases can modulate key regulatory proteins involved in different cellular processes, including metabolism, transcription, cell-cycle progression, cytoskeletal rearrangement and cell movement, proliferation, apoptosis and differentiation. Protein phosphorylation also plays a critical role in intercellular communication during development, in physiological responses, in homeostasis and in the functioning of the nervous and immune systems. Abnormal phosphorylation of proteins can lead to the development of a number of disorders and major diseases, such as rheumatoid arthritis, cardiovascular diseases, immunodeficiency, endocrine disorders, neurodegenerative diseases and cancer [18-20].

Human monoploar spindle 1 (MPS1) kinase (also known as TTK gene) is a dual serine/threonine kinase which plays a dynamic role inspindle kinase assembly checkpoints (SAC) signalling pathways by controlling chromosomal alignment.The function of SAC is to detect incorrectly oriented chromosomes and to orient them by correcting bipolar attachment to the spindle. This signaling cascade includes MPS1, polo, Aurora, Bub, Bubr, *etc*. which help to resolve above mentioned process. Dysfunction or abnormal expression of MPS1 will definitely influence the function of SAC. This defect in SAC may cause chromosomal alignment errors, chromosomal instability, premature mitotic exit and even cell death. MPS1 mRNA dysfunction found in different types of cancer like breast, thyroid, gastric and lung and breast. Several MPS1 inhibitors are reported including cincreasin, SP600125, NMS-P715, AZ3146, MPI-0479605, NMS-P715, CCT251455, *etc.* [21, 22].

Numerous papers have shown that the benzothiazole [23] and thiadiazole [24] nuclei possess a potent anticancer activity against human cancer significantly, killed cells in a tumor-specific manner by inhibiting different targets responsible for the development of tumor.

The molecular hybridization (MH) is a strategy of rational design of new leads based on the recognition of pharmacophoric sub-unities in the molecular structure of two or more known bioactive derivatives, which leads to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates. The molecular hybridization strategy is particularly interesting for the development of new leads for the diseases whose treatment is restricted to few commercial drugs or in cases where bioactive compounds are discovered but presents high toxicity or pharmacokinetic and pharmacodynamic restrictions [25, 26].

Virtual screening is a useful technique to identify new hints. Different types of computational approaches like docking, QSAR *etc*. used for virtual screening. Virtual *in silico* approaches are useful for predicting protein-ligand interaction which gives an idea to identify new potent clinical candidates with fewer side effects [27].

Therefore, the aim of the work was to design hybrid NSAIDs compounds using molecular hybridization approach by linking the main structural unit of the NSAIDs with the benzothiazole and thiadiazole ring (Table **1**) and to perform *in silico* studies.

2. MATERIALS AND METHODS

2.1. Hardware and Software Tool

Virtual screening, Docking and ADMET studies were performed in DELL inspiron 14 with intel core i3 processer, 4GB RAM and 500GB hard disk capacity. The Schrodinger small molecule drug discovery suite was used for performing virtual screening, molecular docking and ADMET studies of design compounds.

2.2. Preparation of Ligands Using Ligprep of Schrodinger

All the structures were prepared in2D sketcher from Schrodinger and then exported to LigPrep. In LigPrep, the structures were energy minimized and 3D geometry corrected. There was no change made in the ionization state. Then, the output file of the compounds were directly used for docking and calculation of ADME properties.

2.3. Protein Preparation

Crystallographic structures of proteins were exported from Protein Data Bank. Three protein structures for TNF-α (PDB ID: 1ZXC), COX-II (PDB id: 5IKR) and protein kinase (PDB id: 5EHO) were downloaded in PDB format. These protein structures were directly used in protein preparation wizard where missing chain residue addition, H-bond addition, removal of water molecules and energy minimization of all structures were done. The output files were used for receptor grid generation.

2.4. Receptor Grid Generation

Receptor grid was generated at the site of ligand present in protein which defines docking site. The size of the grid was similar to the size of the workspace for a ligand which was selected by default $20A^{o}$. The output glide grid file was used for docking.

2.5. Virtual Screening

The screening of the designed compounds was performed using Virtual screening Workflow. LigPrep files were used as input. The glide grid file of each receptor was used for docking. The screenings of compounds were done using QuikProp and Glide docking in Standard precision mode (SP). The preliminary screenings of designed compounds were done using QuikProp and Standard precision mode (SP) of docking using glide function. The screened compounds were again validated using extra precision (XP) mode. At the end of process docking score, H-bond interaction, hydrophobic interaction *etc.* details were collected.

2.6. Bioactivity Prediction

Bioactivity prediction is another computational approach, which is used to determine whether a particular molecule is similar to the known drugs or not by molecular properties and structure features. Bioactivity prediction of all screened compounds were done using Molinspiration online software tool (http://www.molinspiration.com/cgi-bin/properties).

3. RESULTS AND DISCUSSION

3.1. Virtual Screening

We had designed 54 hybrid NSAIDS, which include different derivatives of salicylic acid, aspirin, ibuprofen, naproxen, fenoprofen, and ketoprofen. Molecular hybridization approach was applied to design new compounds by linking the main structural unit of the NSAIDs with the benzothiazole and thiadiazole ring. Structure based virtual screening was performed by applying ADMET filtration and Glide docking in SP mode to find out effective compounds. Docking studies were performed with three different receptors COX-II, TNF-α and protein kinase (MPS1 target). Total 18 compounds were screened, which contains good binding affinity (Table **2**) as well as drug likeliness. The screened compounds were hybrid derivatives of salicylic acid and aspirin. The other derivatives were not screened due to unfavorable properties for drug likeness (due to violations of Lipinski rule of five) and their molecular interactions were not favorable due to more electrostatic charges and rotational penalties (due to more rotatable bonds) of the compounds with the targeted proteins. The structures of all screened compounds were shown in Fig. (**1**). Molecular docking simulations were performed for 18 screened compounds with Glide XP mode to validate ligand more precisely and to find out molecular interactions in comparison with the native ligand.

3.2. Docking Studies of Screened Compounds with the Target TNF-α

The glide score with TNF-α receptor was found in the range of -4.12 to -6.54 with good H-bond interactions. The docking scores of screened compounds were compared with the original ligand present in protein structure [28]. The original ligand bound the target site which exhibits a glide score-5.17. It was observed that compounds 8sa, 9sa, 7sa, 5sa, 6sa and 2sa had higher binding affinity (less docking score) as compared to the standard ligand. The substitution in salicylic acid hybrid derivatives with $-CH_3$, $-OCH_3$ and -Cl on benzothiazole ring at position 5 or 7 were found to be active and aforementioned compounds achieved higher binding affinity. GLY349, GLU406, LEU348, ALA439 and HIS405 were identified as interacting residues for original (standard) ligand. For the screened compounds, ASN389, GLU406, HIS405, ALA351, LEU350, TYR352, ILE438, GLY349 and ALA439 were identified as common interacting residues (Fig. **2A**).

3.3. Docking Studies of Screen Compounds with the Target COX-II

The glide score with COX-II receptor was found in the range between -5.3 to -7 with good H-bond interactions. The docking score of screened compound was compared with the original ligand (mefenamic acid) present in protein structure [29]. The original ligand which binds the target site exhibits a glide score-6.97. Compound 6sa had higher binding affinity (less docking score) as compared to standard drug. ASN389, GLU406, HIS415 and ALA351were identified as interacting residues for original (standard) ligand. For the screened compounds PHE518, ALA516, VAL523, MET522,

Table 2. Docking score of each screened compound with various receptors.

TNF-α		COX-II		MPS1	
Compound Code	**Docking Score (kcal/mol)**	**Compound Code**	**Docking Score (kcal/mol)**	**Compound Code**	**Docking Score (kcal/mol)**
STD	-5.17	STD	-6.97	STD	-7.94
8sa	-6.54	6sa	-7	8sa	-8.84
7sa	-5.74	7sa	-6.5	9sa	-8.78
9sa	-5.68	8sa	-6.5	6sa	-8.68
5sa	-5.34	9a	-6.4	1sa	-8.6
6sa	-5.3	9sa	-6.3	7sa	-8.23
2sa	-5.25	3a	-6.2	6a	-8
4sa	-5.09	6a	-6.2	3sa	-7.92
4a	-4.74	8a	-6.2	4sa	-7.81
2a	-4.52	3sa	-6.1	2a	-7.73
3sa	-4.45	5a	-6.1	3a	-7.72
8a	-4.42	7a	-6.1	2sa	-7.66
3a	-4.37	2a	-5.9	7a	-7.49
1a	-4.26	1sa	-5.8	4a	-7.22
1sa	-4.14	2sa	-5.6	5sa	-7.21
5a	-4.12	5sa	-5.6	1a	-7
6a	-4.12	1a	-5.4	5a	-6.92
9a	-4	4a	-5.4	8a	-6.92
7a	-3.48	4sa	-5.3	9a	-6.73

SER353, TYR355 and PHE357were identified as common interacting residues. Substitution in aspirin and salicylic acid hybrid derivatives with -OCH_3 and -Cl on benzothiazole ring at position 5 or 7 found to be more favorable to bind with receptor (Fig. **2B**).

3.4. Docking Studies of Screen Compounds with the Target Monopolar Spindle Kinase 1 (MPS1)

The glide score with MPS1 receptor was found in the range between 6.73 to -8.84 with good H-bond interactions. The scores of screened compounds were compared with the original ligand present in protein structure [30]. The original ligand bound the target site exhibits glide score-7.94. It was observed that compounds 1a, 4sa, 2a, 7sa, 2sa and 7a had higher binding affinity (less docking score) as compared to standard ligand. Substitution in aspirin and salicylic acid hybrid derivatives with -CH_3 and -Cl on benzothiazole ring at position 5 or 7 more favorable to bind with receptor. GLY605, ILE586, ALA551, VAL536, ILE663, ASP608, PRO673 and ILE607 were identified as interacting residues for original (standard) ligand. For the screened compounds GLY605, ASN606, ILE531, ALA551, ILE5869, MET602, LEU654, VAL539 and PRO673 were identified as common interacting residues (Fig. **2C**).

3.5. Bioactivity Prediction

According to the bioactivity score, if >0 is active; if (-5.0 to -0.0) is moderately active and if <-5.0 is inactive. All the screened compounds have shown moderately active to active score on kinase and enzyme inhibition. Out of all the target predictions, kinase and enzyme inhibition score was found to be the most relevant. The results of bioactivity predictions were mentioned in Table **3**.

3.6. *In Silico* ADMET Study

All the screened compounds pass the Lipinski rule of five and show no violations. Oral absorption of all screened compounds were found in the range of 72-100 percentages. It means that compounds may be orally active. Drug like properties were found in between 0 to 1 star which indicated screened compounds have drug like properties. Results of *in silico* ADMET study in comparison with standard ligands using QuikProp were mentioned in Table **4**.

CONCLUSION

Multiple targeted therapies are very useful for complex diseases like cancer. Virtual screening is powerful technique

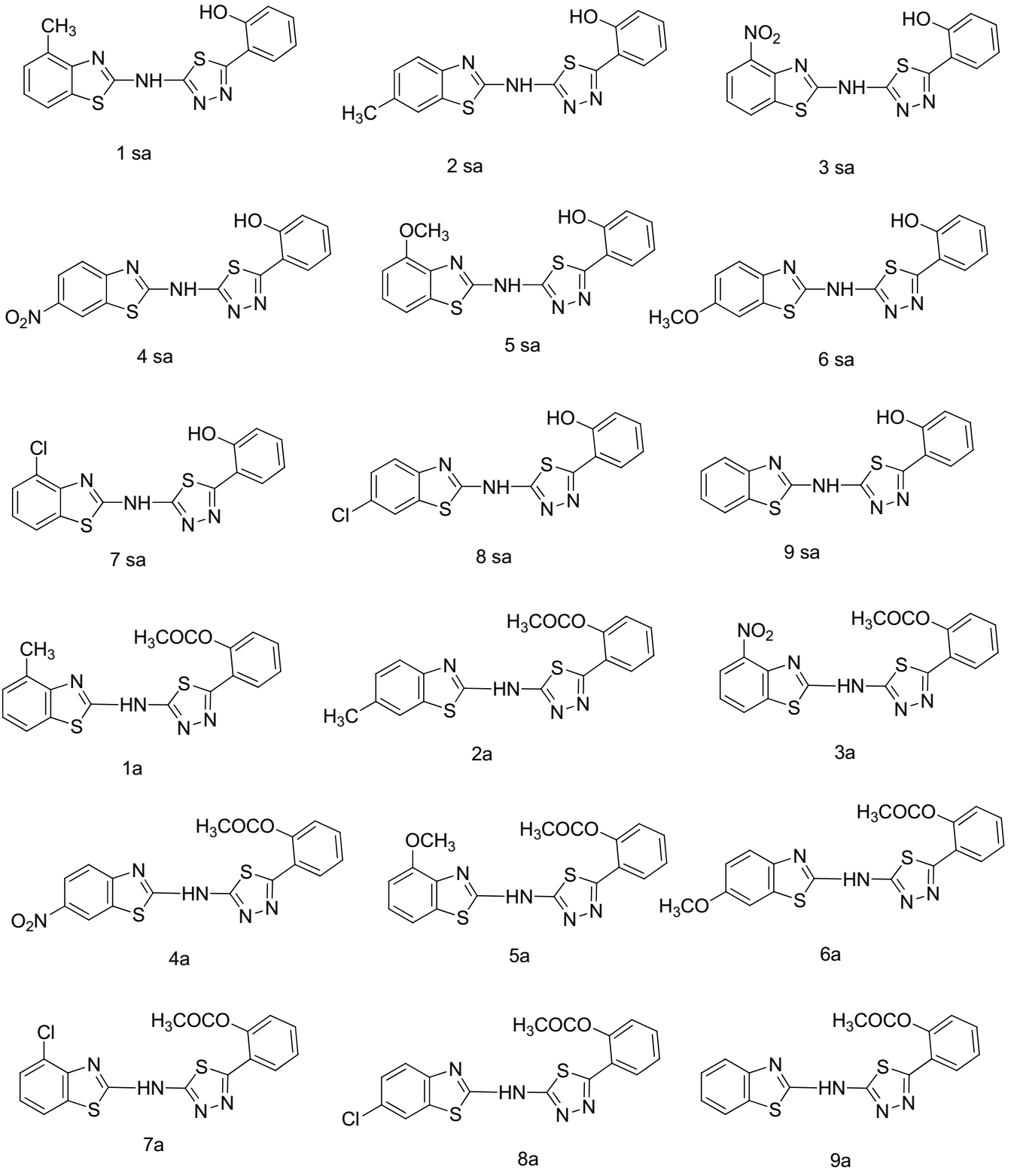


Fig. (1). Structure of all screened compounds.

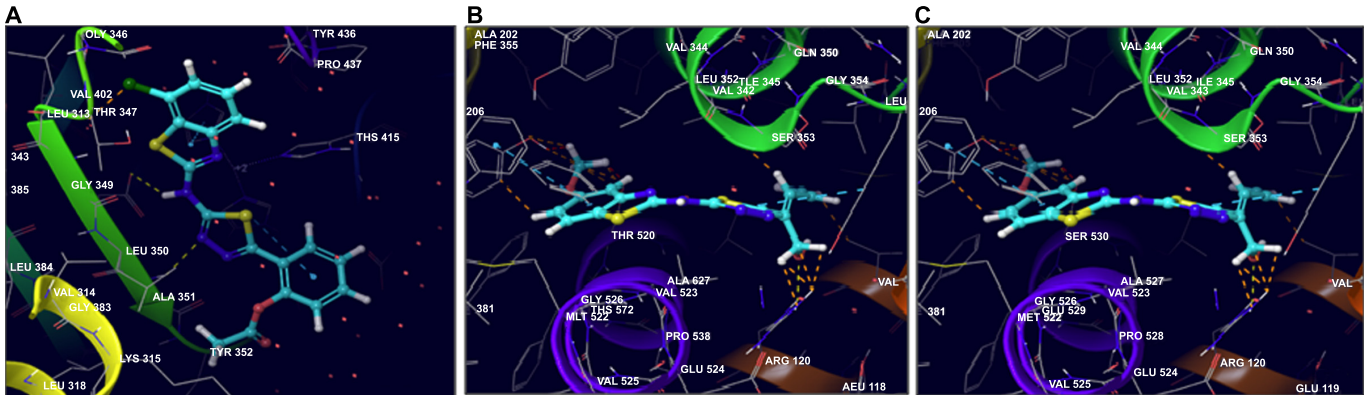


Fig. (2). Showing molecular interactions of screened compounds with different targets. (**A**) TNF-alpha with 7a. (**B**) COX-II with 6SA. **(C)** Protein Kinase with 9SA.

Table 3. Bioactivity prediction of screened compounds.

Code	GPCR	Ion Channel	Kinase Inhibitor	NR Inhibitor	PI	Enzyme Inhibitor
1a	-0.43	-0.75	-0.26	-0.60	-0.73	-0.23
1sa	-0.44	-0.94	0.0	-0.47	-0.86	-0.27
2a	-0.48	-0.64	-0.21	-0.61	-0.62	-0.30
2sa	-0.49	-0.82	0.05	-0.48	-0.74	-0.33
3a	-0.547	-0.63	-0.20	-0.57	-0.69	-0.36
3sa	-0.47	-0.79	0.06	-0.45	-0.45	-0.39
4a	-0.56	-0.58	-0.29	-0.63	-0.68	-0.34
4sa	-0.57	-0.74	0.05	-0.5	-0.78	-0.37
5a	-0,54	-0.72	-0.31	-0.58	-0.70	-0.33
5sa	-0.55	-0.89	0.05	-0.46	-0.80	-0.34
6a	-0.46	-0.63	-0.17	-0.56	-0.6-	-0.27
6sa	-0.46	-0.79	-0.10	-0.44	-0.70	-0.28
7a	-0.45	-0.66	-0.26	-0.63	-0.68	-0.23
7sa	-0.46	-0.3	0.01	-0.51	-0.81	-0.24
8a	-0.42	-0.55	-0.20	-0.61	-0.61	-0.27
8sa	-0.43	-0.71	0.07	-0.48	-0.73	-0.29
9a	-0.45	-0.61	-0.18	-0.61	-0.60	-0.26
9sa	-0.48	-0.78	0.09	-0.49	-0.75	-0.28
STD1	0.21	-0.57	0.23	-0.10	1.34	0.32
STD2	-0.28	-0.20	-0.15	-0.16	-0.50	-0.10
STD3	0.38	0.02	0.96	-0.81	0.04	0.25

GPCR= G-protein Coupled Receptor, NR= Nuclear Receptor Ligand, PI= Protease Inhibitor, STD1= Standard ligand for TNF-alpha, STD2=Standard ligand for COX-II, STD3= Standard ligand for MPS1.

Table 4. ***In silico*** **ADMET predictions of screened compounds.**

Compound	S	MW	HBd	HBa	QPlogP o/w	QP logS	QP PCaco	PHOA	RO5
1a	0	382.454	1	6.5	3.485	-5.598	790.186	100	0
1SA	0	340.417	2	4.75	3.105	-5.037	523.385	93.785	0
2a	0	382.454	1	6.5	3.523	-5.698	790.223	100	0
2SA	0	340.417	2	4.75	3.149	-5.152	524.325	94.06	0
3a	0	413.425	1	7.5	2.499	-5.15	108.706	78.025	0
3SA	1	371.388	2	5.75	2.163	-4.689	72.071	72.858	0
4a	1	413.425	1	7.5	2.518	-5.304	94.279	77.027	0
4SA	1	371.388	2	5.75	2.181	-4.843	62.503	71.859	0
5a	0	398.454	1	7.25	3.271	-5.345	774.263	100	0
5SA	0	356.416	2	5.5	2.895	-4.646	523.157	92.554	0
6a	0	398.454	1	7.25	3.314	-5.364	791.324	100	0
6SA	0	346.421	2	6.45	2.547	-4.209	451.161	89.365	0
7a	0	402.872	1	6.5	3.608	-5.744	774.095	100	0
7SA	0	360.835	2	4.75	3.286	-5.219	524.905	94.868	0
8a	0	402.872	1	6.5	3.706	-5.864	790.215	100	0
8SA	0	350.84	2	5.7	2.916	-4.654	450.814	91.521	0
9a	0	368.427	1	6.5	3.219	-5.137	789.17	100	0
9SA	0	326.39	2	4.75	2.833	-4.602	523.9	92.201	0
STD1	0	398.491	2	9.95	1.192	-3.29	504.09	82.292	0
STD2	0	241.289	1	1.5	3.697	-4.048	398.058	95.124	0
STD3	1	399.497	2	5.5	4.786	-6.645	1662.976	100	0

S (STARS) = Number of property/descriptor values falling outside the 95% range of similar values for known drugs. Recommended value 0-5, **MW** = Molecular Weight, **HBd**= Hydrogen-bond donor, **HBa**= Hydrogen-bond acceptor, **QPlogPo/w =** Predicted octanol/water partition coefficient. Recommended values –2.0 –6.5. **QPlogS =** Predicted aqueous solubility, log S. Recommended values –6.5 –0.5, **QPPCaco =** Predicted apparent Caco-2 cell permeability in nm/sec. Recommended values <25 poor, >500 great, **PHOA=** Predicted Human Oral Absorption on 0 to 100% scale. Recommended values >80% is high <25% is poor, **RO5=** Rule Of Five The rules are: mol_MW < 500, QPlogPo/w < 5, donor HB ≤ 5, and acceptor HB ≤ 10, **STD1**= Standard ligand for TNF-alpha, **STD2**= Standard ligand for COX-II, **STD3**= Standard ligand for MPS1.

to identify new hit molecules which act on multiple targets. It saves the cost and time of drug discovery process. Docking base virtual screening has occupied a prominent role in identifying novel bioactive molecules. In the present work, we had designed 54 molecules, out of these 18 molecules were screened on the basis of binding affinity on various receptors and ADMET filtration. The docking studies were performed on three different types of receptors TNF-α (PDB id: 1ZXC), COX-II (PDB id: 5IKR) and protein kinase (PDB id: 5EHO) whose dysfunction is prominently found in different types of cancer. Bioactivity prediction reveals that all eighteen screened compounds may act through kinase inhibition or enzyme inhibition. All the compounds showed good binding affinity and drug likeliness especially Compounds 2sa, 5sa, 6sa, 7sa showed very good binding affinity with all of three receptors, which indicates screened novel Hybrid NSAIDS may have the ability to reduce inflammation and have the capability to inhibit receptors like TNF-α and protein kinase whose dysfunction gives anti-apoptosis signals for cancer cells. Structural modification can be conducted to improve binding affinity by keeping the same pharmacophore. The study concluded that novel hybrid NSAIDs could further be explored for multiple targeted cancer therapy.

LIST OF ABBREVIATIONS

SP	=	Standard Precision
XP	=	Extra Precision
ADMET	=	Adsorption, Distribution, Metabolism, Toxicity
NSAIDs	=	Non-Steroidal Anti-Inflammatory Drugs
MPS1	=	Monopolar Spindle Kinase1

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Massagué J, Batlle E, Gomis RR. Understanding the molecular mechanisms driving metastasis. Mol Oncol 2017; 11(1): 3-4.

[2] Taniguchi K, Karin M. NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 2018; 18(5): 309-24.

[3] Han R, Hu M, Zhong Q, *et al.* Perfluorooctanesulphonate induces oxidative hepatic damage *via* mitochondria-dependent and NF-κB/TNF-α-mediated pathway. Chemosphere 2018; 191: 1056-64.

[4] Jun JC, Rathore A, Younas H, Gilkes D, Polotsky VY. Hypoxia-inducible factors and cancer. Curr Sleep Med Rep 2017; 3(1): 1-10.

[5] Jänne PA, Gray N, Settleman J. Factors underlying sensitivity of cancers to small-molecule kinase inhibitors. Nat Rev Drug Discov 2009; 8(9): 709-23.

[6] Krishnamachary B, Stasinopoulos I, Kakkad S, *et al.* Breast cancer cell cyclooxygenase-2 expression alters extracellular matrix structure and function and numbers of cancer associated fibroblasts. Oncotarget 2017; 8(11): 17981-94.

[7] Zhang Q, Lenardo MJ, Baltimore D. 30 years of NF-κB: A blossoming of relevance to human pathobiology. Cell 2017; 168(1-2): 37-57.

[8] Yadav MR, Barmade MA, Tamboli RS, Murumkar PR. Developing steroidal aromatase inhibitors-an effective armament to win the battle against breast cancer. Eur J Med Chem 2015; 105: 1-38.

[9] Cristofanon S, Morceau F, Scovassi AI, Dicato M, Ghibelli L, Diederich M. Oxidative, multistep activation of the noncanonical NF-κB pathway *via* disulfide Bcl-3/p50 complex. FASEB J 2009; 23(1): 45-57.

[10] Chen R, Alvero AB, Silasi DA, Mor G. Inflammation, Cancer and Chemoresistance: Taking Advantage of the Toll−Like Receptor Signaling Pathway. Am J Reprod Immunol 2007; 57(2): 93-107.

[11] Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 2007; 117(5): 1175-83.

[12] DasGupta S, Murumkar PR, Giridhar R, Yadav MR. Current perspective of TACE inhibitors: A review. Bioorg Med Chem 2009; 17(2): 444-59.

[13] Vane JR, Warner TD. Nomenclature for COX-2 inhibitors. Lancet 2000; 356(9239): 1373-4.

[14] Dubois RN, Abramson SB, Crofford L, *et al.* Cyclooxygenase in biology and disease. FASEB J 1998; 12(12): 1063-73.

[15] Cao Y, Prescott SM. Many actions of cyclooxygenase−2 in cellular dynamics and in cancer. J Cell Physiol 2002; 190(3): 279-86.

[16] Rayyan Y, Williams J, Rigas B. The role of NSAIDs in the prevention of colon cancer. Cancer Invest 2002; 20(7-8): 1002-11.

[17] Sulciner ML, Gilligan MM, Zetter BR, Panigrahy D. Inflammation and Cancer: The Role of Lipid Signaling in the Continuum Between Two Ends of the Tumor Spectrum. In: *Biomarkers of the Tumor Microenvironment*. Cham: Springer; Germany, 2017; pp. 167-93.

[18] Wilhelm M, Schlegl J, Hahne H, *et al.* Mass-spectrometry-based draft of the human proteome. Nature 2014; 509(7502): 582-7.

[19] Cohen P. Protein kinases - the major drug targets of the twenty-first century? Nat Rev Drug Discov 2002; 1(4): 309-15.

[20] Gross S, Rahal R, Stransky N, Lengauer C, Hoeflich KP. Targeting cancer with kinase inhibitors. J Clin Invest 2015; 125(5): 1780-9.

[21] Xie Y, Wang A, Lin J, *et al.* Mps1/TTK: A novel target and biomarker for cancer. J Drug Target 2017; 25(2): 112-8.

[22] Liu X, Winey M. The MPS1 family of protein kinases. Annu Rev Biochem 2012; 81: 561-85.

[23] Kumar V, Sharma S, Husain A. Synthesis and *in vivo* Anti-inflammatory and analgesic activities of oxadiazoles clubbed with benzothiazole nucleus. Int Curr Pharm J 2015; 4(12): 457-61.

[24] Özdemir A, Sever B, Altıntop MD, *et al.* Synthesis and evaluation of new oxadiazole, thiadiazole, and triazole derivatives as potential anticancer agents targeting MMP-9. Molecules 2017; 22(7): 1109.

[25] Viegas-Junior C, Danuello A, da Silva Bolzani V, Barreiro EJ, Fraga CA. Molecular hybridization: a useful tool in the design of new drug prototypes. Curr Med Chem 2007; 14(17): 1829-52.

[26] Xie L, Huang J, Chen X, *et al.* Design, synthesis and biological evaluation of novel rapamycin benzothiazole hybrids as mTOR targeted anti-cancer agents. Chem Pharm Bull (Tokyo) 2016; 64(4): 346-55.

[27] Kumar V, Krishna S, Siddiqi MI. Virtual screening strategies: Recent advances in the identification and design of anti-cancer agents. Methods 2015; 71: 64-70.

[28] Levin JI, Chen JM, Laakso LM, *et al.* Acetylenic TACE inhibitors. Part 2: SAR of six-membered cyclic sulfonamide hydroxamates. Bioorg Med Chem Lett 2005; 15(19): 4345-9.

[29] Orlando BJ, Malkowski MG. Substrate-selective inhibition of cyclooxygeanse-2 by fenamic acid derivatives is dependent on peroxide tone. J Biol Chem 2016; 291(29): 15069-81.

[30] Innocenti P, Woodward HL, Solanki S, *et al.* Rapid discovery of pyrido [3, 4-d] pyrimidine inhibitors of monopolar spindle kinase 1 (MPS1) using a structure-based hybridization approach. J Med Chem 2016; 59(8): 3671-88.