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DRUG DISCOVERY

Virtual screening of few novel Sulindac derivatives as multi-targeted agents

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ABSTRACT

The immense contribution of structure based drug design in the field of drug discovery is noteworthy. Molecular docking methodology has drawn considerable attention in it. Observing multiple affinities in a single chemical entity is one of the biggest challenges in modern drug discovery. One of the drug with this feature is Sulindac. Owing to its affinity towards multiple targets, PPAR-γ, β-secretase and COX-2, several derivatives were designed and subsequently docked to develop binding mode within the active site of the respective targets. The comparison in the binding energy was made considering the cocrystal associated with each target. All the docked compounds were evaluated for their drug likeliness. Parameters, like binding energies and distance between the conformer and active site residues were considered. Majority of compounds exhibited significant affinity towards the enzyme COX-2. However, for PPAR-γ, promising interaction was noticed for several compounds, including AKS 10, AKS 27, AKS33. Highest

affinity was found in AKS 33 and AKS 34 towards *β*-secretase. The outcome of the *in-silico* approach leaves a great scope for optimization as most of the Sulindac derivatives exhibit considerable affinity towards the respective targets, hence requires further elaboration towards synthesis and biological evaluation.

Article keywords: PPAR-*γ*, *β*-secretase, COX-2, Molecular docking.

1. INTRODUCTION

Sulindac is popularly known for its antiinflammatory property. The therapeutic benefit obtains, by biotransformation within the liver to produce the active entity, sulfides from sulfinylindene, responsible for the efficacy [1]. Sulindac shows quite higher activity as Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists [2]. PPAR-γ is a type II nuclear receptor mainly present in adipose tissue and muscle. The genes activated by PPAR-γ mainly increases adipogenesis and lipid uptake phenomenon [3]. Activation of genes regulating fatty acid metabolism and lipogenesis shows insulin sensitizing effects of anti-diabetic drugs. PPARγ helps in secretion of adipocytokines from adipose tissue which mediates insulin action in peripheral tissues [4].

The therapeutic application of Sulindac has already been extended towards alzheimer's disease, a neuro degenerative disorder [5]. Alzheimer's disease is caused due to deposition of amyloid beta (Aβ) protein on brain cells, causing neuronal damage, atrophy of cortical and subcortical areas leading to dementia. Amyloid precursor protein (APP) is converted to amyloid beta peptides by protease activity of Beta (*β*) Secretase (BACE1) enzyme, via enzymatic cleavage [6]. The affected individuals suffered from memory loss which cannot be recovered easily. Sulindac derivatives exhibits promising affinity towards *β* secretase [7], through nonspecific binding mechanism and thus might become an effective Anti-Alzheimer's agents.

Sulindac derivatives is already known for its anti-inflammatory effect by inhibiting COX-2 enzyme [8].

Considering its diversity towards several enzymes, binding mode within the respective active sites needs to be established. Molecular docking is one of the best way to rapidly screen large chemical databases and subsequently identify the most promising one for further illustration. A number of docking programs like, DOCK [9], GOLD [10], AutoDock [11], FlexX [12], QXP [13], GLIDE [14] and ICM [15] were developed for the purpose of execution. Docking serves two important tasks, first one is the assessment of all possible orientations and geometry of the ligands associated within the binding site of the receptor, called "Search Algorithm", which emphasizes on ligand and receptor flexibility. The second one is the prediction of binding affinity between two molecules and thereby detection of binding energies of the complex via several mathematical functions, called "Scoring Functions". Low RMSD and low energy values determine the correct binding pose, which can be predicted by scoring functions. Drug tolerance and resistance have become an annoying event to the prescribers. Owing to this, fixed dose combinations are quite often being considered for therapy, leading to development of noncompliance to the patient. Therefore, several strategies have been considered to narrow down the combination. One of the recent endeavors is to amalgamate multiple drugs in a single dosage form. But in the recent past, drug regulatory bodies took a massive step in restricting such kind of practices. The *in-silico* study aims at establishing the biochemical behavioral aspect of multiple targets toward a single chemical entity. From an overall perusal of the preamble, it is observed that Sulindac, being a highly active NSAID, can develop equal affinity towards other targets like PPAR γ and *β*-Secretase. The aforementioned discussion highlighted the importance of docking methodology in developing the preliminary concept of ligand-target interactions.

2. MATERIALS AND METHODS

It is a well known fact that Sulindac exhibits affinity towards multiple targets, though the biomolecular mechanism of Sulindac as a multi-targeted agent has not yet been established till date. In a process of developing a wide understanding of this fact, a series of fifty compounds (AKS 1-AKS 50) was designed considering Sulindac as a template. The design is exclusively based on atomic resolution structure of Sulindac, therefore alteration is of atom-based, which includes the side chain patterns, substituting the ring heteroatoms, expanding or minimizing the parent ring and determine their affinity in three different targets namely: PPAR Gamma, *β*-Secretase and COX-2 using docking methodology. The selection of COX-2 as one of the target is purely based on the conventional usage of Sulindac as anti-infammatory agent, whereas the other two targets namely PPAR γ and β-Secreatse were chosen considering the latest scientific revealation of Sulindac pertaining to its affinity towards the respective targets. On the basis of the initial outcome, the study may be continued for synthesis and biological evaluations. Considering the topological description of the chosen targets and 2D poseview of cocrystal within the active site of PPAR Gamma, *β* Secretase and COX-2, (Figure 1) different diversified derivatives of Sulindac have been designed.

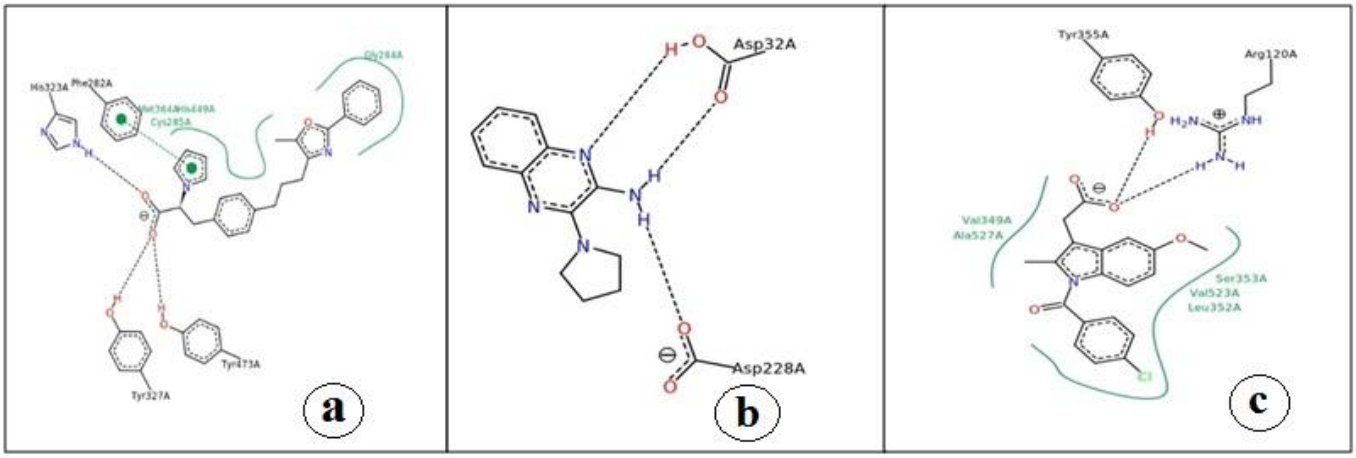


Figure 1: **a**- 2D poseview of native ligand (Co-crystal) within the active site of PPAR Gamma;**b**- 2D poseview of native ligand (Co-crystal) within the active site of *β* Secretase: **c**- 2D poseview of native ligand (Co-crystal) within the active site of COX-2

Target (macromolecule) Modelling

All the macromolecules namely PPAR Gamma, *β* Secretase and COX-2 were modelled using MGL Tools 1.5.6 (The Scripps Research Institute, Molecular Graphics Laboratory, 10550 North Torrey Pines Road, La Jolla, CA, 92037, USA) in Windows based HP system (1.70 GHz processor, 4GB RAM, 465.76GB Hard disk, 64 bit OS). The macromolecules considered for the study were fetched from Brookhaven Protein Data Bank (PDB; https://www.rcsb.org). It was observed that, PPAR Gamma Receptor Complex (PDB Entry: 2Q8S) possess L92; (2s)-3-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propyl]phenyl}-2-(1H-pyrrol-1-yl)propanoic acid as its primary ligand, whereas EV2; 3-pyrrolidin-1-ylquinoxalin-2-amine was traced within the active site of the other enzyme, Beta Secretase (PDB Entry: 3HW1). The final target is Cyclooxygenase-2(COX-2) enzyme (PDB Entry: 4COX) holding IMN; 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

All the receptors were then subjected to Python Molecular Viewer. In order to rule out the interference of water molecules present all around the crystal, all were removed at the initial stage. Bond orders were assigned and the missing hydrogen atoms added. Partial atomic charges of all the atoms were calculated using Gasteiger-Marsili method. Kollman united atom charges were assigned, non-polar hydrogens were merged, and rotatable bonds were assigned. All the proteins procured from the databank were in the form of pdb, which was further converted "pdbqt" assigning the charges (q) and atom type to Autodock4 (t). Gasteiger partial charges are assigned to each atom of the above said receptors.

Validation of Docking Protocol

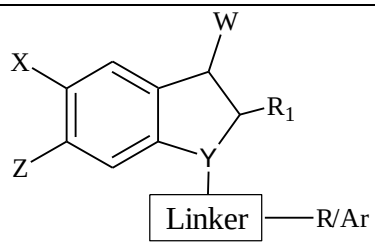
The most effective method of assessing the accuracy of a docking procedure is to confirm how closely the lowest energy pose predicted by the scoring function resembles an experimental binding pattern as developed through X-ray crystallography. In the current study, docking procedure was validated by removing cocrystals from the respective binding sites and redocking all to the binding pocket of respective macromolecules. It is observed that a very good agreement between the localization of the inhibitors upon docking. The root mean square deviations (RMSD) between the predicted conformation and the observed X-ray crystallographic conformation of all the compounds was less than 1.3 Å for each target.

Ligand modelling

2D structures of various ligands were sketched in Chemsketch (ACD 2012: Advanced Chemistry Development, Inc.8 King Street East, Suite 107, Toronto, Ontario, Canada M5C 1B5). Using PRODRG server [16], all the 2D structures were transformed into their 3D form with file extension of pdb. The partial atomic charges were assigned to each and every ligands and assigned to Autodock type, subsequently converted into 'pdbqt' form.

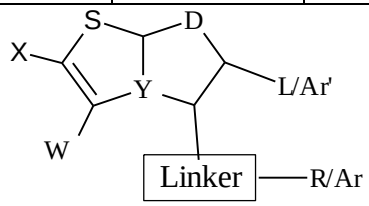
Different derivatives of Sulindac that are taken in consideration for docking, are given in Table 1

Table 1 Ligands Designed for Docking Analysis

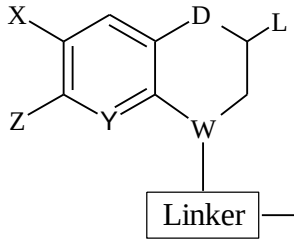


Compound code	Y	Linker	R/Ar	C_2-C_3 Hybridization	R_1	W	X	Z
AKS 1	C	=CH-	4-Heptylphenyl	Sp^3	CH_3	Ethanoic acid	F	NH_2
AKS 2	C	-	4-(3-methyl)-hexylphenyl	Sp^3	CH_3	Ethanoic acid	F	OH
AKS 3	C	=CH-	4-(3,4-dimethyl)-pentylphenyl	Sp^3	CH_3	Ethanoic acid	-O- CH_3	Cl
AKS 4	N	-C=O	4-Heptylphenyl	Sp^3	CH_3	Ethanoic acid	F	-
AKS 5	N	-C=O	4-(3,4-dimethyl)-pentylphenyl	Sp^3	-	Ethanoic acid	-COOH	OH
AKS 6	N	-C=O	4-Heptylphenyl-(2-ethenyl)	Sp^3	CH_3	-OH	Cl	-
AKS 7	N	-C=O	4-heptylphenyl	Sp^3	-	-	F	NH_2
AKS 8	N	$-CH_2$	Phenyl-4-[3-(N-hydroxycarbamoyl) propyl]	Sp^3	-	Ethanoic acid	F	NH_2
AKS 9	N	-C=O	phenyl-4-(propyl-propionate)	Sp^3	-	Ethanoic acid	F	NH_2
AKS 10	N	-C=O	Phenyl-4-(propyl-sulfinylmethyl)	Sp^3	-	Ethanoic acid	Cl	OH
AKS 11	N	-C=O	Phenyl-4-(methoxybutyl)	Sp^3	-	Ethanoic acid	F	NH_2
AKS 12	N	$-CH_2$	Phenyl-4-(chlorobutyl)	Sp^3	-	Ethanoic acid	F	NH_2
AKS 13	N	-C=O	Phenyl-4-carboxypropyl	Sp^3	-	Ethanoic acid	F	NH_2
AKS 14	N	-NH-	Phenyl-4-(methyl sulfinylpropyl)	Sp^3	-	Ethanoic acid	Cl	NH_2
AKS 15	N	$-CH_2$	phenyl-4-[(4-carbamoyl)butyl]	Sp^3	-	Ethanoic acid	Cl	NH_2
AKS 16	C	=CH-	1H-naphthyl	Sp^2	$-CH_3$	Ethanoic acid	-O-CH_3	-
AKS 17	C	=CH-	1,1'-biphenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 18	C	=CH-	4-cyclohexyl-phenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 19	C	=CH-	4-propylphenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 20	C	=CH-	4-pentylphenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-

AKS 21	C	=CH-	4-methylthio-ethylphenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 22	C	=CH-	4'-methylthio-1,1'-biphenyl	Sp^2	$-CH_3$	Ethanoic acid	$-O-CH_3$	-
AKS 23	C	=CH-	2',4'-difluoro-1,1'-biphenyl	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 24	N	-C=O	3-(1-butenyl)-phenyl	Sp^2	-	Ethanoic acid	$-NH-CH_3$	-
AKS 25	C	=CH-	Phenyl-4-[3-(N-hydroxycarbamoyl) propyl]	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 26	C	-C=O	4-(N-methylcarbamoyloxyethyl)Phenyl	Sp^2	-CH3	Ethanoic acid	F	-
AKS 27	C	-C=O	Phenyl-4-(methylsulfonylpropyl)	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 28	C	=CH-	Phenyl-4-(methyloxycarbonyl propyl)	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 29	C	=CH-	Phenyl-4(4-carboxy-3-hydroxycyclohexyl)	Sp^2	$-CH_3$	Ethanoic acid	F	-
AKS 30	C	-C=O	4-(hex-1-oyl)-phenyl	Sp^2	-	Ethanoic acid	$-O-CH_3$	$-O-CH_3$
AKS 31	C	-C=O	4-[(4-methylsulfinyl)cyclohexyl]	Sp^2	-	Hexane	-COOH	F
AKS 32	C	=CH-	2-pentyl-1,2,3,4-tetrahydronaphth-2-yl	Sp^2	$-CH_3$	Ethanoic acid	F	F
AKS 33	N	$-CH_2$	4-(1-methylhexyl)-phenyl	Sp^2	-	Hydroxy methyl	-COOH	-
AKS 34	N	-	ethyloxycarbonyl-methyl	Sp^2	-	Hydroxy methyl	-COOH	-

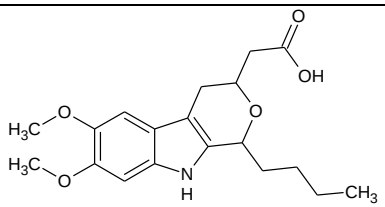


Compound code	Y	Linker	R/Ar	L/Ar'	D	X	W
AKS 35	-CH	$-CH_2$	Hexyl	-	$-CH-CH_2-COOH$	-	-Cl
AKS 36	N	-	Carboxymethyl	4-hydroxyphenyl	NH	F	CH_3
AKS 37	-CH	-	Carboxymethyl	Cl	NH	F	CH_3
AKS 38	-CH	=CH-	4-(1,3-dihexenyl)-phenyl	-	$-CH-CH_2-COOH$	$-O-CH_3$	-

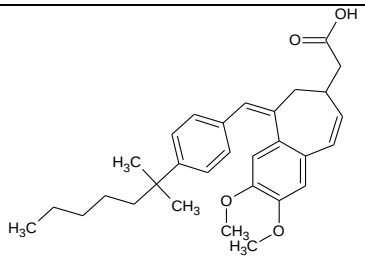


Compound code	W	Linker	R/Ar	L	D	X	Z	Y
AKS 39	C	=CH-	4-pentyl-phenyl	-	-CH- COOH	F	-	C
AKS 40	N	-C=O	(4-chloro-3-propyl)phenyl	-	-CH- COOH	-O-CH_3	-	N
AKS 41	-CH	-	1-methyl-hept-1,5dienyl	-COOH	-O-	-OCH_3	-OCH_3	C
AKS 42	-CH	-	1-methyl-hept-1,5dienyl	-CH_2-C_6H_4-(p-CH_3)	-O-	-COOH	-	C
AKS 43	-CH	-CH_2	methyl-3-ethylthiophenyl	-CH_2-COOH	-O-	-OCH_3	-OCH_3	C
AKS 44	-CH	-	N-hydroxy-carbamoyl	-CH_2-COOH	-O-	-OCH_3	-OCH_3	C
AKS 45	-CH	-	Methylthio-carbonyl-methyl	-CH_2-COOH	-O-	-COOH	F	C

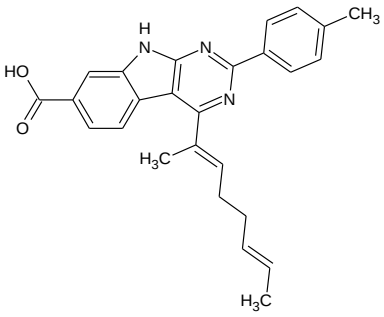
SOME ADDITIONAL COMPOUNDS



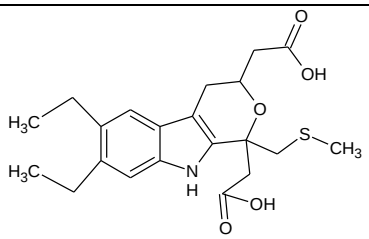
AKS 46



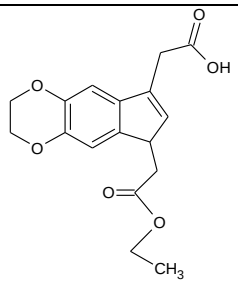
AKS 47



AKS 48



AKS 49



AKS 50

Molecular docking analysis:

All the docking analysis were performed in Autodock Vina [17], installed in a HP system (1.70GHz processor, 4GB RAM, 465.76GB Hard disk, 64 bit OS). Autodock vina was designed by Dr. Oleg Trott at the Scripps Research Institute. For the docking procedure, a grid spacing of 1 Å and 24 X 24 X 24 number of points was considered as default. Vina yielded 9 energetically significant conformers for each ligand. The binding mode and interactions were analyzed for the significant compounds with their virtually bioactive conformer(s).

3. RESULTS AND DISCUSSION

Drug discovery, in its neonatal stage witnessed several limitations. Initial design, mostly relied on scientific literature. With the advent of bioinformatics, a paradigm shift has been observed for the last few decades. Structure based drug design has drawn considerable interest to the medicinal chemists, owing to its magnified characteristics in revealing the confirmation space within the active site of a biological target. As a part of this process the contribution of molecular docking methodology is inexplicable.

Considering the above fact the present study has been developed for an understanding of the mode of interaction of few novel Sulindac derivatives with their complimentary fragments which constitute the active site of multiple targets. Three different targets namely: PPARγ, β-Secretase and COX-2, were considered for the study. The chemical anomaly, as observed in Sulindac, a series of 50 Sulindac derivatives (AKS 1 to AKS 50) were designed, and subsequently subjected all the compounds for docking study. The docking output is given in Table 2.

Table 2: Docking output of compounds (AKS 1-AKS 50)

MACROMOLECULES									
COMPOUND	**PPAR GAMMA (2Q8S)**			**β SECRETASE (3HW1)**			**COX-2 (4COX)**		
	c*	**BE[μ]**	***d*[κ]**	***c****	**BE[μ]**	***d*[κ]**	***c****	**BE[μ]**	***d*[κ]**
STANDARD	3	-10.3	2.1	8	-9.0	2.9	4	-11.1	2.0
AKS 1	5	-7.9	8.8	7	-8.4	4.6	1	-11.5	7.8
AKS 2	1	-10.5	6.5	4	-9.0	3.7	9	-9.1	5.2
AKS 3	2	-9.2	12.8	3	-8.2	3.4	3	-9.3	11.8
AKS 4	1	-8.0	3.3	8	-6.6	5.8	5	-7.8	2.4
AKS 5	7	-7.5	2.2	6	-7.8	3.4	9	-8.2	2.2
AKS 6	1	-9.5	8.2	1	-8.7	5.5	5	-9.6	2.6
AKS 7	9	-7.9	3.7	8	-8.0	3.9	8	-8.6	6.1
AKS 8	6	-8.2	3.7	6	-8.1	4.8	4	-9.1	3.1

AKS 9	1	-9.3	3.9	9	-6.8	5.6	2	-8.9	3.1
AKS 10	1	-9.7	2.1	9	-7.5	3.8	2	-9.3	2.2
AKS 11	8	-7.0	3.5	5	-7.5	6.4	2	-8.7	2.1
AKS 12	3	-7.8	3.6	3	-7.5	3.2	1	-9.5	3.6
AKS 13	1	-9.1	2.6	9	-7.2	6.2	1	-9.4	2.2
AKS 14	2	-9.0	2.3	5	-7.2	3.5	4	-8.3	2.2
AKS 15	4	-7.7	3.1	8	-7.7	7.8	5	-8.0	2.3
AKS 16	3	-9.3	3.7	7	-8.1	3.3	3	-9.4	2.7
AKS 17	2	-10.4	4.9	2	-9.6	4.4	2	-8.9	2.4
AKS 18	2	-10.4	4.9	8	-8.6	5.1	4	-9.0	2.4
AKS 19	1	-9.2	4.2	9	-7.7	4.0	7	-8.4	2.8
AKS 20	2	-9.3	4.2	9	-7.5	4.2	2	-8.7	3.0
AKS 21	6	-8.3	3.0	2	-8.4	4.3	3	-8.6	2.4
AKS 22	4	-10.1	3.3	1	-9.3	5.8	1	-9.9	2.6
AKS 23	3	-11.1	4.1	7	-9.1	4.2	6	-7.1	3.0
AKS 24	2	-9.0	4.6	8	-7.0	3.2	3	-8.9	2.8
AKS 25	2	-10.4	2.4	2	-9.1	4.2	8	-7.0	3.2
AKS 26	4	-9.4	2.3	4	-7.9	4.1	2	-8.3	2.9
AKS 27	2	-9.8	2.0	5	-8.0	5.1	5	-7.6	2.8
AKS 28	8	-9.2	2.1	7	-8.0	5.2	1	-9.6	4.7
AKS 29	7	-9.1	2.4	8	-8.5	3.9	7	-8.7	2.2
AKS 30	2	-8.3	2.4	5	-6.9	3.7	1	-8.2	2.5
AKS 31	4	-7.7	4.9	1	-8.0	3.3	2	-8.2	2.0
AKS 32	1	-8.7	8.7	4	-7.3	3.3	1	-8.4	2.5
AKS 33	7	-7.8	1.8	3	-7.8	3.0	3	-8.5	2.9
AKS 34	5	-6.5	2.0	3	-6.3	3.0	7	-7.1	2.2
AKS 35	5	-8.6	8.9	9	-8.1	4.4	1	-11.2	8.5
AKS 36	3	-7.7	3.3	8	-6.2	3.5	6	-7.2	2.1
AKS 37	1	-7.0	2.2	3	-5.5	4.8	6	-6.8	2.1
AKS 38	6	-7.9	4.2	3	-7.2	4.3	3	-8.2	3.1
AKS 39	6	-8.6	4.1	9	-6.8	4.5	4	-9.7	5.0
AKS 40	1	-8.9	4.5	7	-7.6	3.5	4	-7.0	4.6
AKS 41	3	-6.6	10.7	3	-6.6	4.1	2	-7.5	2.7
AKS 42	2	-8.7	2.0	5	-6.8	3.4	6	-8.9	3.1
AKS 43	9	-7.6	2.2	7	-6.7	3.3	8	-7.3	2.8
AKS 44	1	-8.0	2.4	2	-6.7	3.1	1	-7.9	2.2
AKS 45	2	-8.0	1.9	7	-6.5	3.3	7	-8.2	2.2
AKS 46	9	-6.7	2.1	7	-6.5	3.2	6	-6.7	2.5
AKS 47	8	-6.9	13.3	1	-7.6	3.5	4	-7.8	2.1
AKS 48	8	-7.2	4.9	3	-7.9	5.4	9	-6.9	7.4
AKS 49	4	-6.5	6.2	6	-6.5	3.7	7	-6.2	2.5
AKS 50	2	-8.3	3.7	8	-6.4	3.2	1	-9.4	2.1

[* : Conformer closest to the active site residue]

[μ : Binding Energy (Kcal/mole)]

[κ : Distance from the active site residue (Å)]

Autodock successfully reproduced the experimental binding conformations of each native ligand in the binding pocket of all the macromolecules with an acceptable root mean-square deviation (RMSD) of less than 1.3Å.

Multiple criteria have been set to assess the quality of docked compounds. Docking energy was one of it. The other criteria were found to be the closeness between the active site residues and the conformer lying in its proximal vicinity. The priority is given to

the distance criterion. For a compound to be highly active, it should lie in an approximate distance of ≤3.0 Å within the active site, whereas for moderately active compound, a distance of 3.1-7.0 Å within active site was set, finally, the least active compounds are the one which exceeds the distance of 7.0 Å.

In PPARγ, compounds, AKS 5, AKS 10, AKS 13, AKS 14, AKS 21, AKS 25, AKS 26, AKS 27, AKS 28, AKS 29, AKS 30, AKS 33, AKS 34, AKS 37, AKS 42, AKS 43, AKS 44, AKS 45, AKS 46 were considered to be highly active, as all of them complied the default criteria set for the assessment of accurately docked compounds. One of them, AKS 10 [5-chloro-6-hydroxy-1-{4-(3-methylsulfinyl-propyl) phenyl-methanone} 2,3-dihydroxy-indol-1H-3-ethanoic acid], is shown in Figure 2.

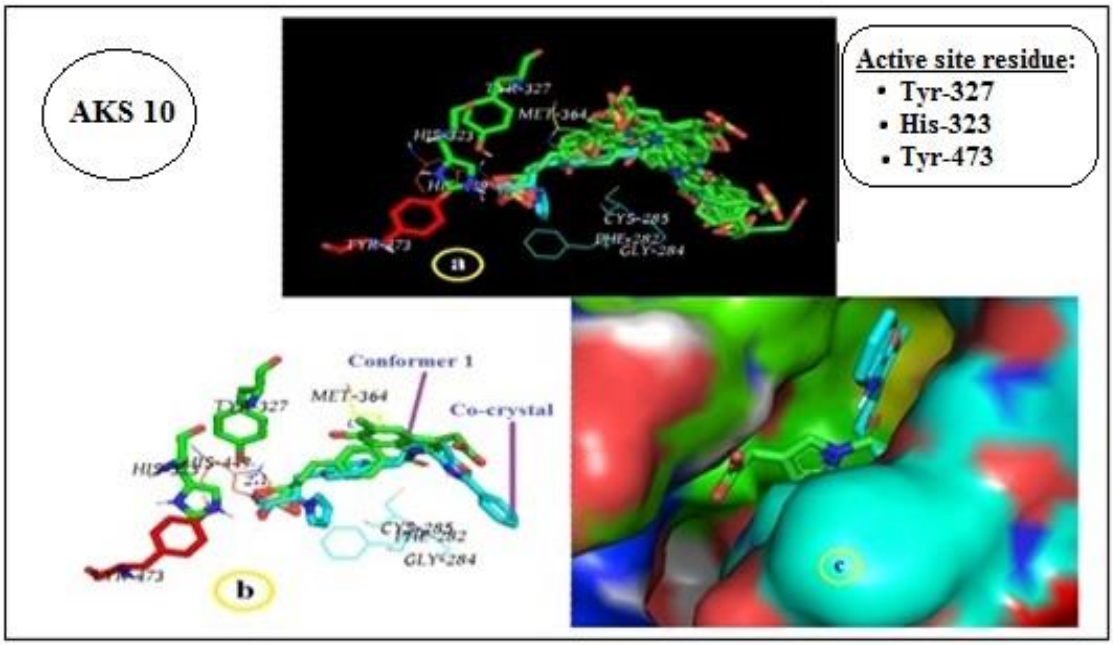


Figure 2 Highly active compound of PPARγ; **a**- Cluster of conformers within the active site of PPAR γ (2Q8S); **b**- Stereoview of best active conformer (conformer 1) of AKS 10; **c**- Molecular surface view of active conformer 1 of AKS 10

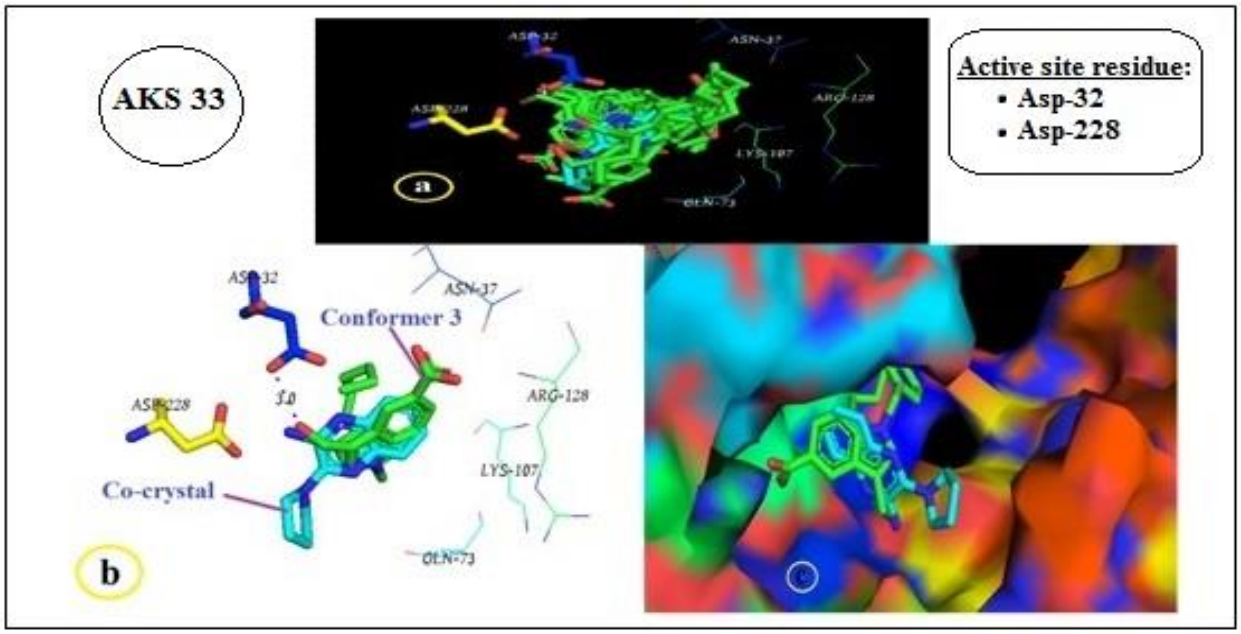


Figure 3 Highly active compound of β secretase; **a**- Cluster of conformers within the active site of β secretase (3HW1); **b**- Stereoview of best active conformer (conformer 3) of AKS 33; **c**- Molecular surface view of active conformer 3 of AKS 33

All the stated compounds were found to be in their most favourable orientation, lying closest to the active site residues of PPARγ i.e. (TYR-327, HIS-323, TYR-473). Figure 2 clearly indicates that the sulfinyl group present in compound AKS 10 developed an affinity

towards the phenolic hydroxyl group of TYR-327 by means of hydrogen bonding. Compounds AKS 2, AKS 4, AKS 7, AKS 8, AKS 9, AKS 11, AKS 12, AKS 15, AKS 16, AKS 17, AKS 18, AKS 19, AKS 20, AKS 22, AKS 23, AKS 24, AKS 31, AKS 36, AKS 38, AKS 39, AKS 40, AKS 48, AKS 49, AKS 50 were considered to be moderately active in PPARγ. Remaining compounds were considered to be least active.

In β secretase, compounds AKS 33 and AKS 34 are the highly active compounds and lies in close vicinity to active site residues (ASP-32, ASP-228). Amongst them, AKS 33 [3-hydroxymethyl-1-{4-(1-methyl-hexyl) phenyl-methyl} indol-1H-5-methanoic acid] is shown in Figure 3.

It depicts that the ethanolic-OH group attached to indole moiety of AKS 33, shows close affinity with terminal COOH group of ASP-32, in the active site domain of β secretase, by means of hydrogen bonding. Compounds AKS(1-14), AKS(16-32), AKS(35-50) fall under the category of moderately active ones. AKS 15 is the only compound listed, which have least affinity.

In COX-2, compounds, AKS 4, AKS 5, AKS 6, AKS 10, AKS 11, AKS (13-24), AKS 26, AKS 27, AKS (29-34), AKS 36, AKS 37, AKS 41, AKS (43-47), AKS 49, AKS 50 are highly active compounds and lie closely to the active site residues (ARG-120, TYR-355). Amongst them AKS 11 [6-amino-5-fluro-1-{4-(4-methoxy-butyl)phenyl-methanone}2,3-dihydroxy-indol-1H-3-ethanoic acid] is shown in Figure 4.

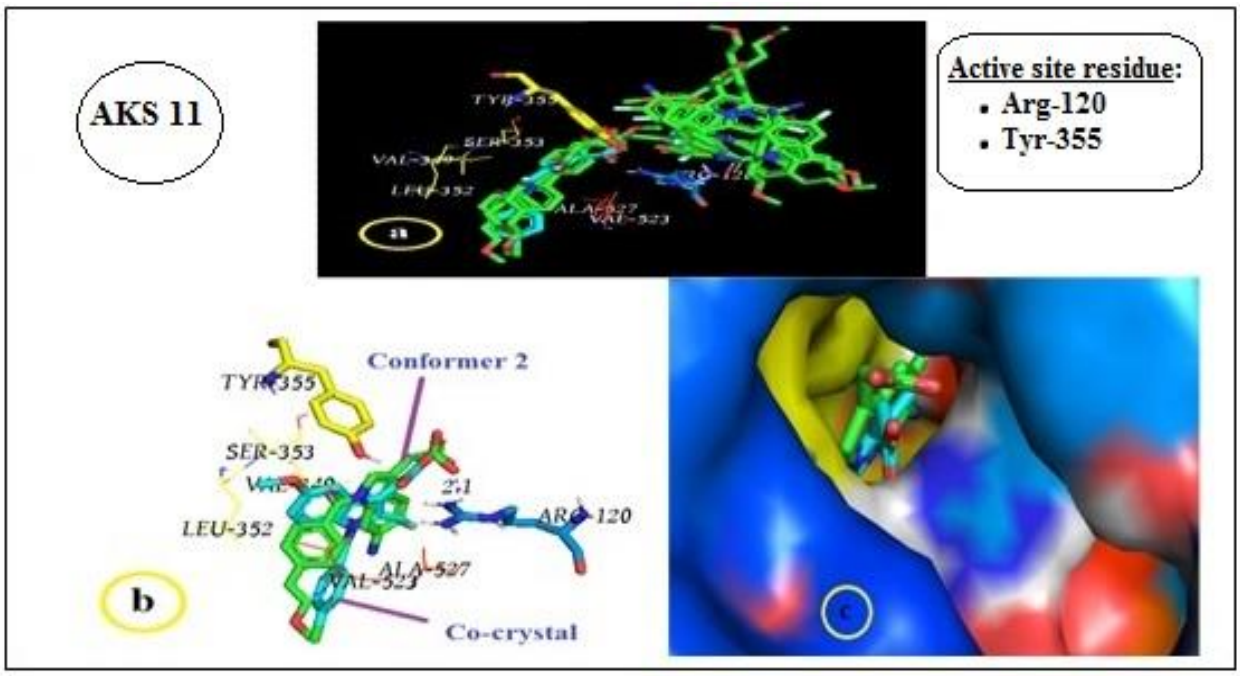


Figure 4 Highly active compound of COX-2; **a**- Cluster of conformers within the active site of COX-2 (4COX); **b**- Stereoview of best conformer (conformer 2) of AKS 11; **c**- Molecular surface view of active conformer 2 of AKS 11

It denotes that the ethanoic acid group, attached to the indoline system of AKS 11, lies very close to the active site domain and shows strong dipole-dipole interaction with active site residue ARG-120. Compounds AKS 2, AKS 7, AKS 8, AKS 9, AKS 12, AKS 25, AKS 28, AKS 38, AKS 39, AKS 40, AKS 42 are found to be moderately active, as per the given set criteria. Compounds AKS 1, AKS 3, AKS 35 and AKS 48 are least active.

4. CONCLUSION

Molecular docking study was conducted for a series of fifty compounds, in order to assess the binding affinity of each one of them towards multiple targets as observed in the drug, Sulindac. All the derivatives were developed considering the structural features of Sulindac. After an exhaustive docking operation, it is clearly observed that significant interaction took between molecules. The putative active sites present in three respective targets, PPAR-γ, *β* secretase and COX-2, attracted most of the compounds efficiently. With respect to the closeness between the pharmacophoric groups of each compound and active site residues, most of it turned up significantly. Such a promising outcome leaves a huge scope in continuing the study in different dimensions to make it scientifically and biologically significant, which will provide benefit to the mankind.

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Authors' contributions

Arka Das*: Contributed in gathering information and nurturing those into a suitable research work.

Sudipta Nandi: Operated the docking software to dock each compound within the active site of the respective targets considered for the study.

Kingshuk Das: All the structures were drawn and optimized for the study was done by this author.

Subhasis Banerjee: Developed the idea and execute the ideas into a productive work.

Ethical issues

Not applicable, as far as research work is concerned.

Further Information

No such organization was involved in funding the project.

Conflict of Interest

The authors declare no conflict of interests.

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