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Original Article

Insilico Molecular Design of Novel Substitued Biaryl Ethenes for the Treatment of Polycystic Ovarian Syndrome

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ABSTRACT

This research manuscript presents a comprehensive study on the design and evaluation of novel ligands for the Retinoid X Receptor Alpha (RXRA), a promising therapeutic target in the treatment of Polycystic Ovary Syndrome (PCOS). Leveraging insights from the existing literature, a scaffold library was constructed consisting of 100 newly designed ligands featuring pharmacophoric characteristics such as hydrogen bond acceptors, hydrophobic cores, and aromatic rings. Molecular docking studies were conducted using SwissDock 2.0 to assess the binding affinities and interactions of these ligands with RXRA (PDB ID: 4N8R). The results identified several highly active hits, including RXRA57, RXRA52, and RXRA93, which demonstrated favourable docking scores. Subsequently, these ligands underwent optimization for drug-likeness based on Lipinski's rule of five and ADMET properties, confirming their potential as effective modulators for PCOS treatment. The findings underscore the therapeutic relevance of RXRA modulation and highlight the efficacy of the newly designed ligands in addressing PCOS symptoms, paving the way for future *in vitro* and *in vivo* evaluations.

Introduction

PCOD (Polycystic ovary Disease) is a condition and PCOS (Polycystic ovary syndrome) is a symptom. A pattern of Symptoms belonging to a particular disease is defined as a Syndrome.

Ovary of normal women who is in the age of her reproductive years has a volume of around 4-6 ml of each ovary and have a folded structure like a walnut, but if a woman is diagnosed with PCOS, her ovaries get enlarged and bulky with having more than 10 ml of volume, thus it Starts producing a high quantity of androgens normal ovulating ovaries contain fluid-filled sacs called Follicles, with variations in size from 1 to 30 millimeters, which depends on the phase of the menstrual cycle. The individual sac or follicle contains a tiny egg, which never matures enough to trigger ovulation. While in the polycystic Ovary, there are more than 12 small follicles, measuring 2 to 9 millimeters in diameter, and are usually arranged in a 'pearl-necklace'

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manner around the periphery. So, as the name suggests, poly means many, in polycystic ovary syndrome there are many small cysts like sacs that are filled with fluids and grown inside the ovaries, and they do not need to be removed surgically [1].

Materials and Methods

Selection of Target

Retinoid X receptor alpha (RXR-alpha), also known as NR2B1 (nuclear receptor subfamily 2, group B, member 1) is a nuclear receptor that in humans is encoded by the RXRA gene. Retinoic acid receptors (RARs) are nuclear receptors, primarily found within the nucleus, that function as ligand-activated transcription factors, activated by retinoic acid, a derivative of vitamin A. They form heterodimers with retinoid X receptors (RXRs) and bind to specific DNA sequences in retinoid-responsive target genes [2].

There are three subtypes of RARs: RARα, RARβ, and RARγ, each with distinct expression patterns and functions. RARs are expressed in a cell-specific manner, with RARα being expressed in immune cells, RARβ in various tissues, and RARγ in skin and other tissues.

Structure of Retinoid X Receptor-Alpha

Protein name: RXRA

Classification: signalling

protein chains: A

Total structure weight: 55 kDa

Length: 462 residues

Gene name: 1.RXR-alpha

Function: A group of proteins that regulate gene expression by binding to specific DNA sequences.

Types: RXR receptor has 462 amino acids with three common isoforms (RARα, RARβ, and RARγ) have essential role in regulation of gene regulation. They contain unique residues that differs from others [3].

Table 1: Unique residue and distinctive features of RXR receptors.

S. No.	Type	Unique Residue	Distinctive Feature
1	*RXRα*	R225, K229, and E233 in the LBD	A longer NTD compared to RXRβ and RXRγ
2	*RXRβ*	Q221, S225, and T229 in the LBD	A shorter NTD compared to RXRα
3	*RXRγ*	V223, A227, and L231 in the LBD	A distinct loop structure in the LBD

To distinguish each subtype based on residue structure

LBD: Focus on the ligand-binding pocket and surrounding residues. RXRα has a more hydrophilic pocket, while RXRβ and RXRγ have more hydrophobic pockets.
DBD: Although the DBD is highly conserved among RXR subtypes, subtle differences in residue composition and structure can be observed.
NTD: The length and residue composition of the NTD vary among subtypes, with RXRα having a longer NTD [4].

Mechanism of action

Retinoid X Receptor Alpha (RXRA) plays a crucial role in the development and progression of PCOS. RXRA Agonist Mechanism stimulating RXRA activity can alleviate PCOS symptoms by:

1. Reducing androgen production: Decreasing RXRA-mediated androgen synthesis.
2. Improving insulin sensitivity: Enhancing insulin signaling pathways.
3. Restoring ovulatory function: Normalizing ovulation and menstrual cycles.

Stimulating RXRA activity offers a promising therapeutic strategy for PCOS treatment. Further research will help elucidate the mechanisms underlying RXRA's role in PCOS and develop effective treatments [5].

Selection of PDB ID

Protein Data Bank (PDB) is a crystallographic database for three-dimensional structural data of large biological molecules such as proteins, Nucleic acid and Complex assemblies. Ultimately human trials will help to understand the potential risks and benefits of these novel approaches across a number of diseases [6].

Some of the recent and efficient PDB enzyme targets with low resolution were selected and further evaluated by its Resolution value, R Free. R value and optimized crystal ligand interaction details. Some of the efficient PDB file receptors for RxRa with low resolution were selected (4N8R) from RCSB protein data bank and their active site were identified.

PPB Id for RxRa is listed below with their resolutions.

Table 2: List of PDB for RxRa.

S. No.	Code	Resolution
1	4N8R	2.03A^{O}
2	8PP0	1.90 A^{O}
3	2P1T	1.80 ^{O}

Pharmacophore Identification

Pharmacophore modeling correlates the biological activity with the spatial arrangement of various features in set of active analogues. When reviewing the eminent journals and research articles, Hydrophobic region, Hydrogen bond acceptor, Aromatic ring, Polar region was identified as the best model for designing RXRA agonist [7].

Key Residues

- **Arg271**: Forms hydrogen bonds with ligands.
- **Ser289**: Forms hydrogen bonds with ligands.
- **Phe313**: Participates in hydrophobic interactions with ligands.
- **Trp305:** Participates in hydrophobic interactions with ligands.

Incorporate hydrophobic groups to interact with the hydrophobic pocket. Incorporate hydrogen bond acceptors or donors to interact with Arg271 and Ser289. Incorporate aromatic groups to interact with Phe313 and Trp305 [8].

Construction of Virtual Library

A library consisting of nearly 100 new lead molecules as potent RXRA agonist was designed based on the knowledge of the binding interaction of the ligand with the protein and also the common pharmacophoric features necessary for the biological activity of a molecule. Chemical features like Hydrogen bond acceptor (HBA), Hydrogen bond donor (HBD), and aromatic ring features were used to screen the database [9].

Novelty

Checking novelty of the ligands using PubChem software.

Pass Prediction

PASS (Prediction of Activity Spectra for Substances) is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule [10].

Lead Optimization

Drug likeness screening

Drug likeness is qualitative concept used in drug design for how druglike substances is to be an effective drug Dug likeness properties was performed for all the newly designed *RXRA* modulators by using online *software Molinspiration* and ADMETLAB software and the results were tabulated.

Docking studies

All the designed ligands were subjected to docking studies using *Swiss dock 2.0* software and the results were discussed below.

Results and Discussion

Construction of Virtual Library

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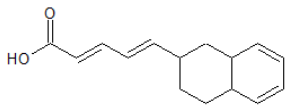
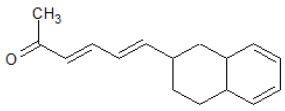
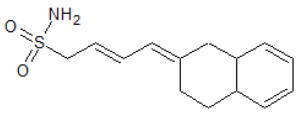
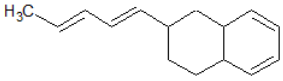
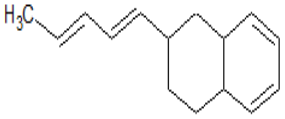
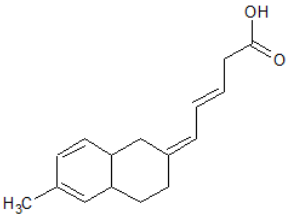
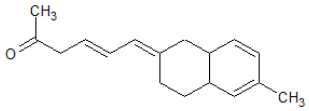
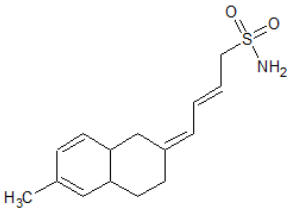
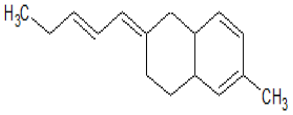
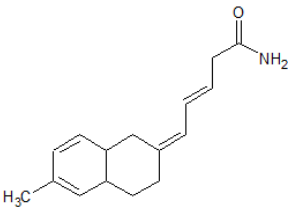
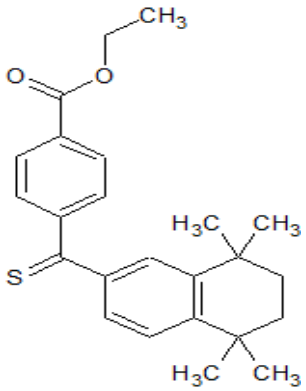
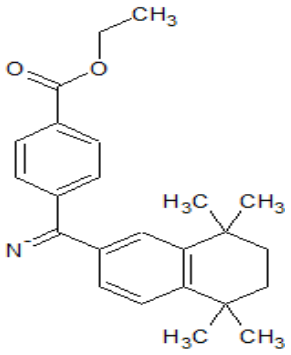
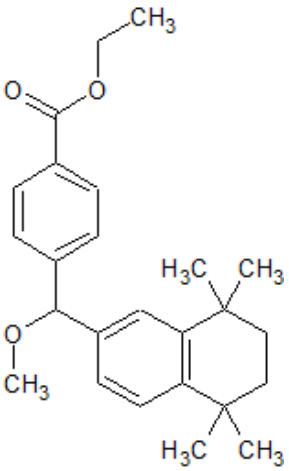
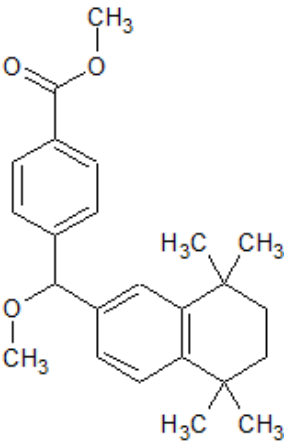
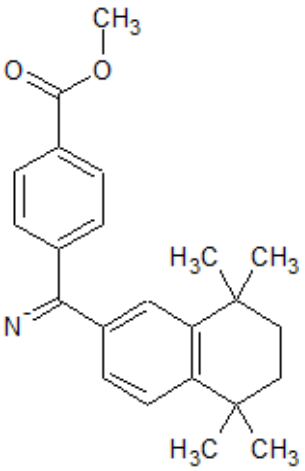
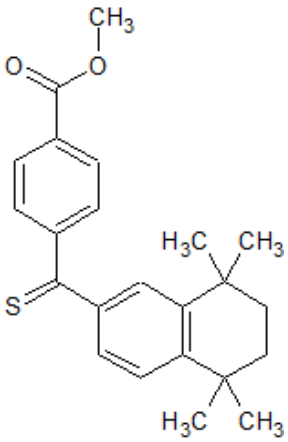
RXRA1 	**RXRA2** 	**RXRA3** 	**RXRA4** 
RXRA5 	**RXRA6** 	**RXRA7** 	**RXRA8** 
RXRA9 	**RXRA10** 	**RXRA11** 	**RXRA12** 
RXRA13 	**RXRA14** 	**RXRA15** 	**RXRA16** 

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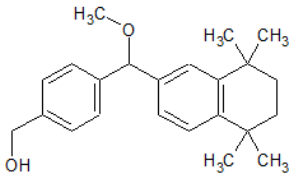	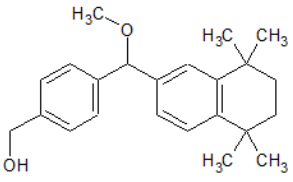	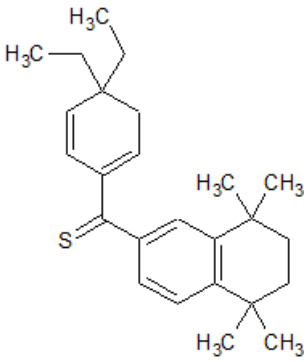	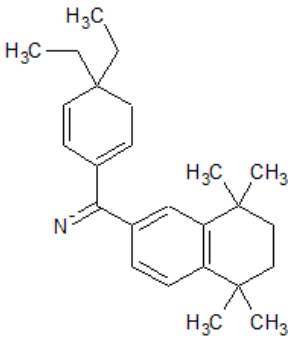
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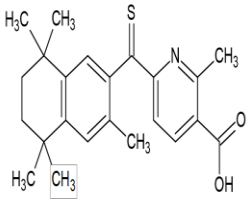	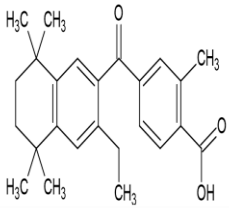	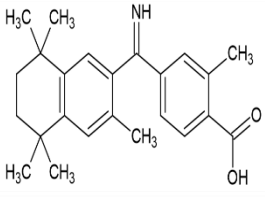	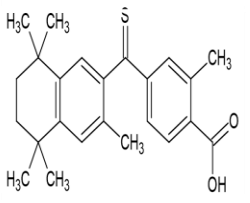
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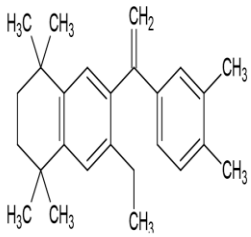	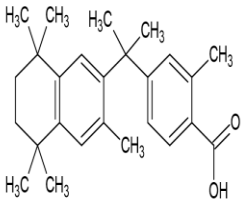	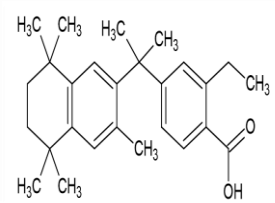	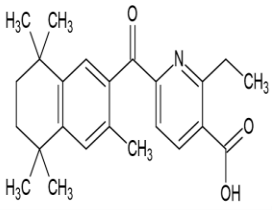
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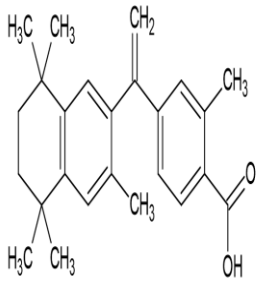
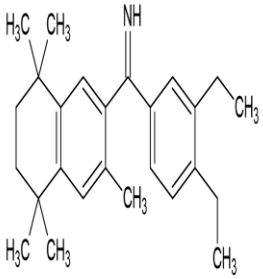
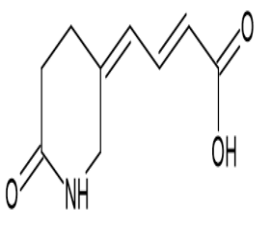
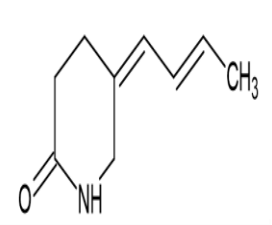
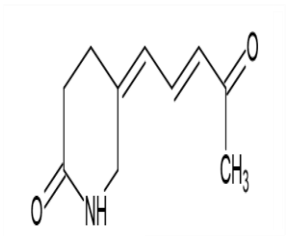
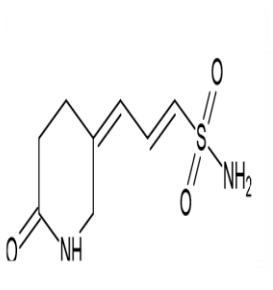
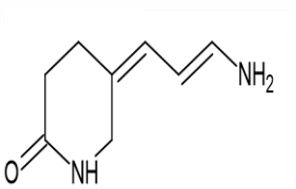
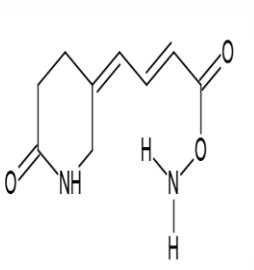
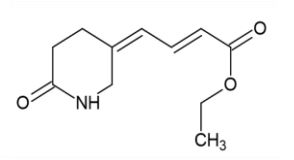
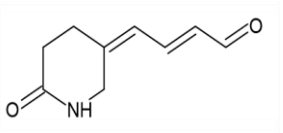
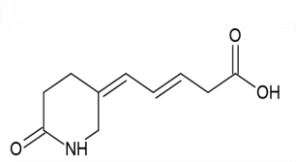
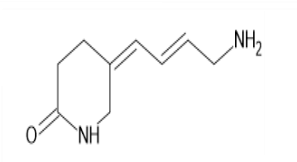
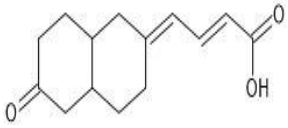
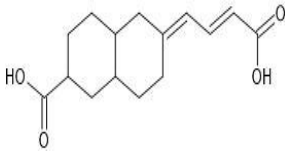
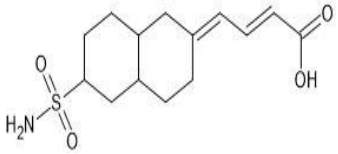
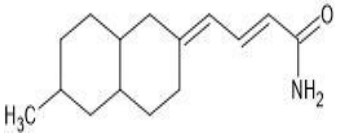
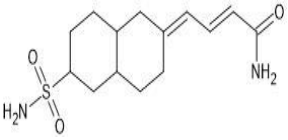
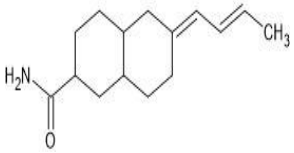
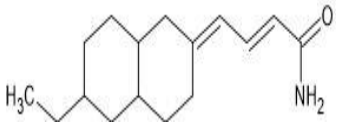
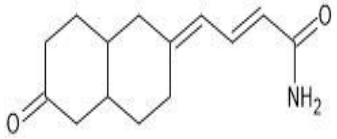
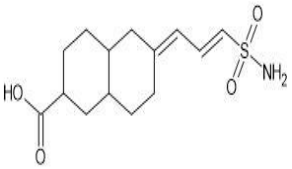
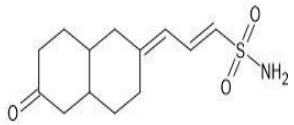
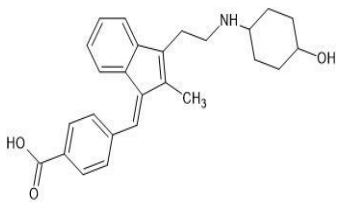
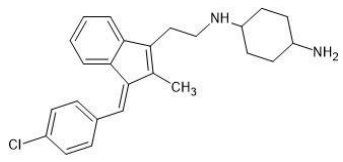
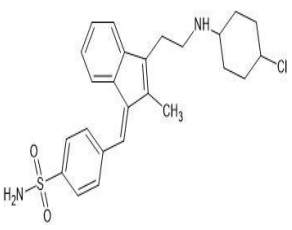
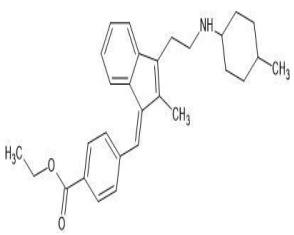
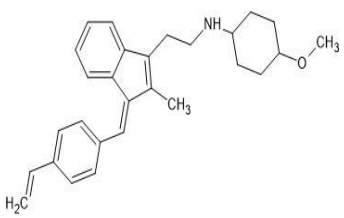
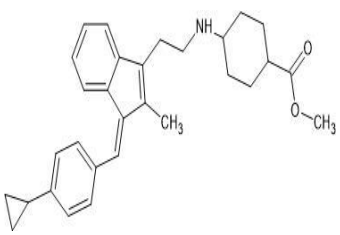
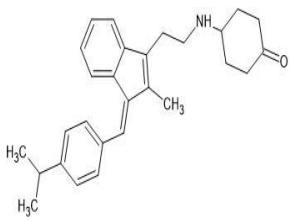
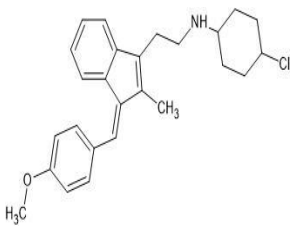
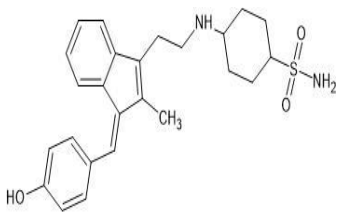
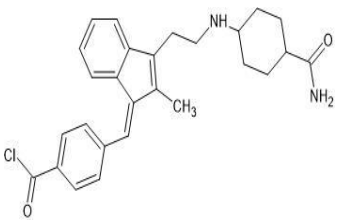
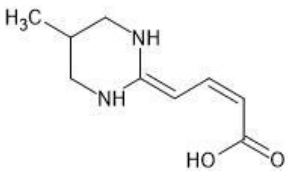
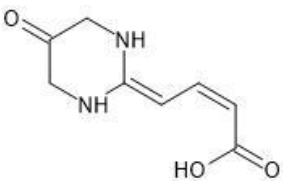
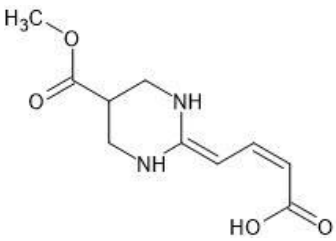
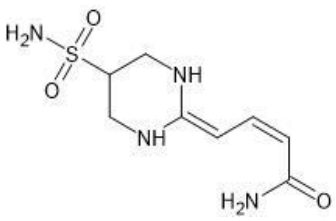
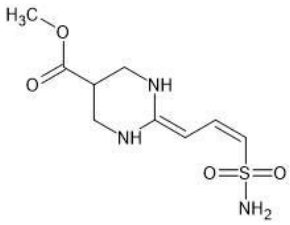
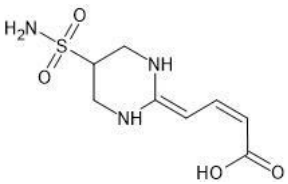
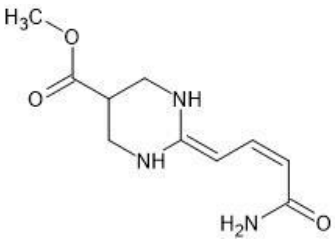
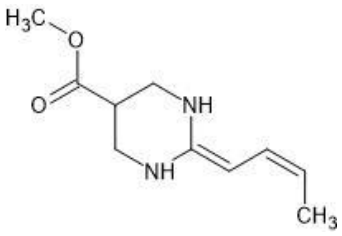
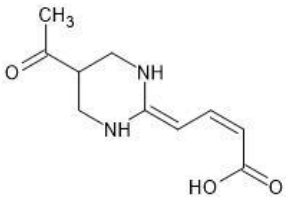
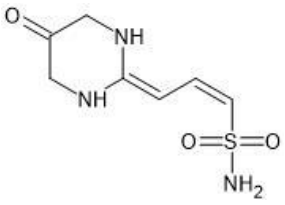
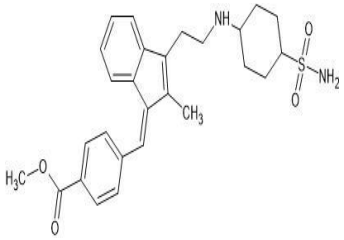
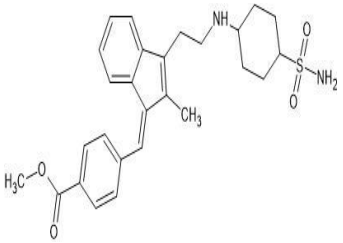
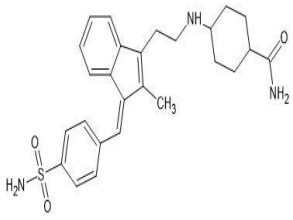
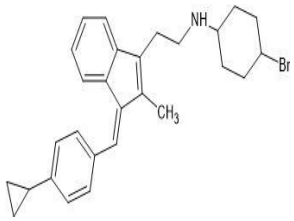
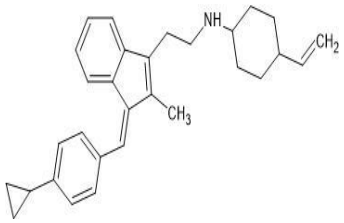
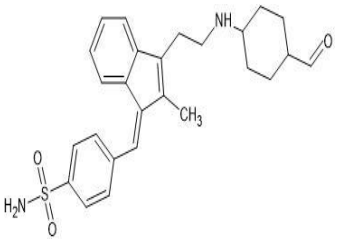
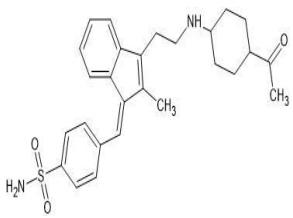
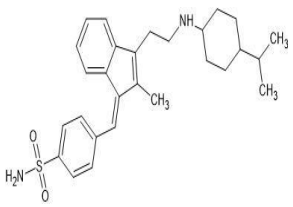
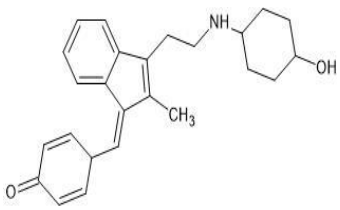
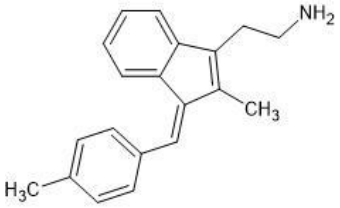
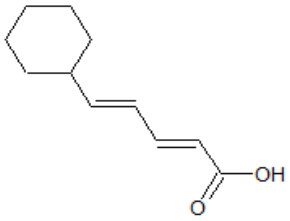
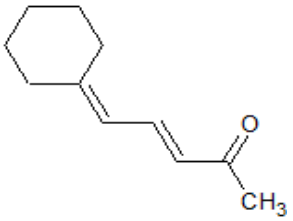
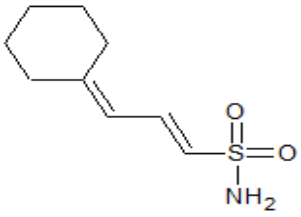
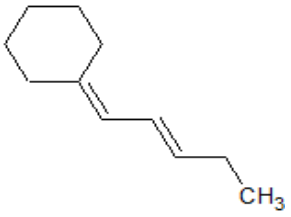
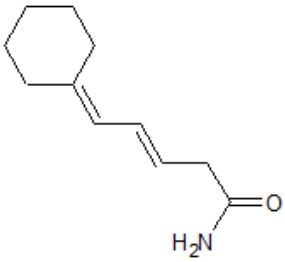
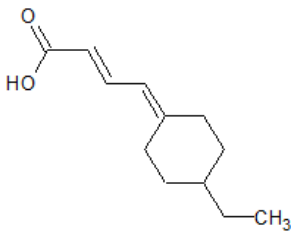
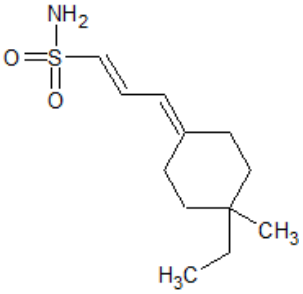
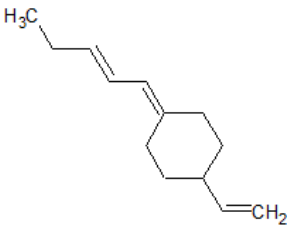
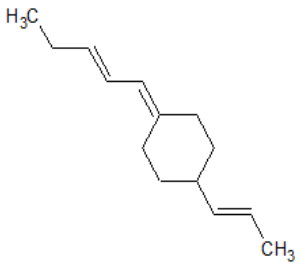
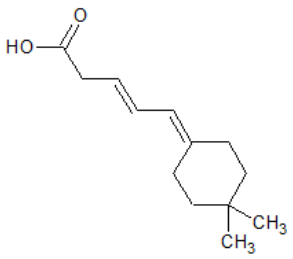
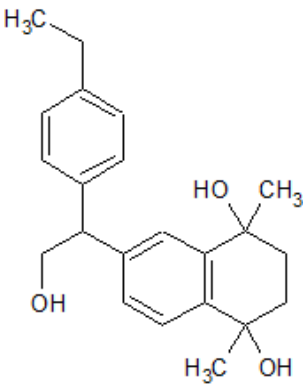
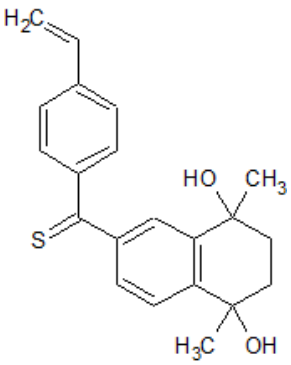
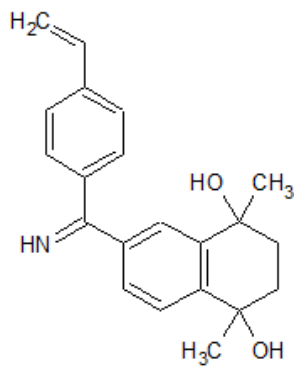
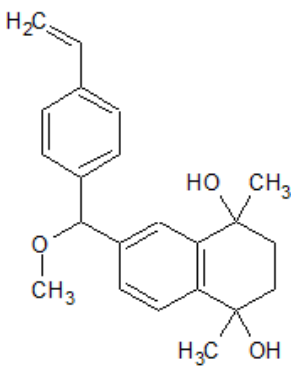
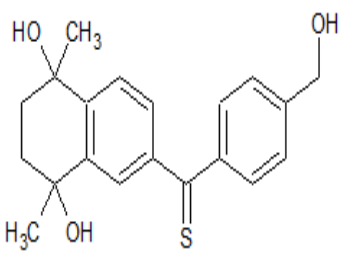
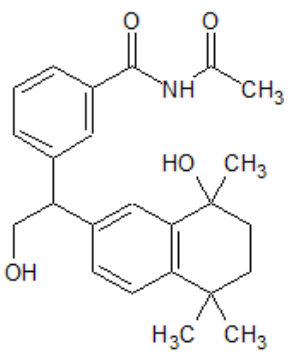
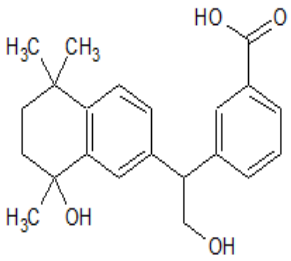
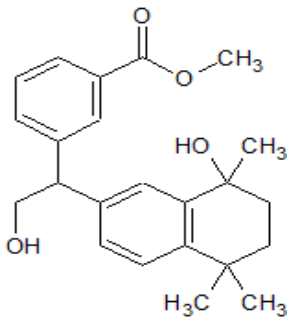
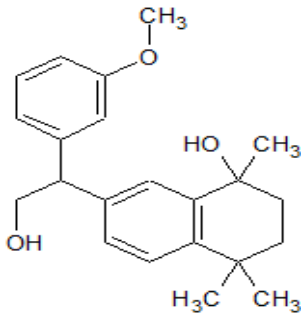
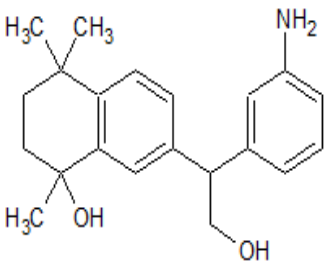
			

RXRA33 	**RXRA34** 	**RXRA35** 	**RXRA36** 
RXRA37 	**RXRA38** 	**RXRA39** 	**RXRA40** 
RXRA41 	**RXRA42** 	**RXRA43** 	**RXRA44** 
RXRA45 	**RXRA46** 	**RXRA47** 	**RXRA48** 
RXRA49 	**RXRA50** 	**RXRA51** 	**RXRA52** 
RXRA53 	**RXRA54** 	**RXRA55** 	**RXRA56** 

RXRA57 	**RXRA58** 	**RXRA59** 	**RXRA60** 
RXRA61 	**RXRA62** 	**RXRA63** 	**RXRA64** 
RXRA65 	**RXRA66** 	**RXRA67** 	**RXRA68** 
RXRA69 	**RXRA70** 	**RXRA71** 	**RXRA72** 
RXRA73 	**RXRA74** 	**RXRA75** 	**RXRA76** 

RXRA77 	**RXRA78** 	**RXRA79** 	**RXRA80** 
RXRA81 	**RXRA82** 	**RXRA83** 	**RXRA84** 
RXRA85 	**RXRA86** 	**RXRA87** 	**RXRA88** 
RXRA89 	**RXRA90** 	**RXRA91** 	**RXRA92** 

RXRA93	RXRA94	RXRA95	RXRA96
			
RXRA97	**RXRA98**	**RXRA99**	**RXRA100**
			

Lead Optimization

Molinspiration®

Drug likeliness assessment all the 100 newly designed ligand molecules were subjected to drug likeliness assessment and the compounds with conformance of Lipinski rule are chosen.

The physicochemical and biological property of designed ligands were calculated using Molinspiration® software.

Table 3: Physicochemical properties of 100 designed ligands.

Compound	Log P	Mol. Wt	TPSA	noHNH	nON	No. of Rotatable Bonds	No. of Violations
RXRA1	1.83	230.31	37.30	1	2	3	0
RXRA2	2.45	228.34	17.07	0	1	3	0
RXRA3	1.42	265.38	60.16	2	3	3	0
RXRA4	2.96	200.32	0	0	0	2	0
RXRA5	1.31	229.32	43.09	2	2	3	0
RXRA6	3.18	244.33	37.30	1	2	3	0

RXRA7	3.48	242.36	17.07	0	1	3	0
RXRA8	2.45	279.40	60.16	2	3	3	0
RXRA9	4.54	214.35	0	0	0	2	0
RXRA10	2.67	243.35	43.09	2	2	3	0
RXRA11	7.11	380.55	26.30	0	2	5	1
RXRA12	3.39	362.49	48.58	0	3	5	0
RXRA13	6.65	380.53	35.54	0	3	6	1
RXRA14	6.28	366.50	35.54	0	3	5	1
RXRA15	3.02	348.47	48.58	0	3	4	0
RXRA16	6.74	366.53	26.30	0	2	4	1
RXRA17	5.44	338.49	29.46	1	2	4	1
RXRA18	2.19	320.46	42.50	1	2	3	0
RXRA19	7.91	366.61	0	0	0	4	1
RXRA20	4.19	348.55	22.27	0	1	4	0
RXRA21	5.74	381.54	50.19	1	3	3	1
RXRA22	6.82	378.51	54.37	1	3	4	1
RXRA23	6.15	363.50	61.15	2	3	3	1
RXRA24	6.89	380.55	37.30	1	2	3	1
RXRA25	8.17	346.56	0.00	0	0	3	1
RXRA26	7.28	378.56	37.30	1	2	3	1
RXRA27	7.75	392.58	37.30	1	2	4	1
RXRA28	5.77	379.50	67.26	1	4	4	1
RXRA29	6.85	362.51	37.30	1	2	3	1
RXRA30	7.96	361.57	23.85	1	1	4	1
RXRA31	0.04	181.19	66.40	2	4	2	0
RXRA32	1.17	151.21	29.10	1	2	1	0

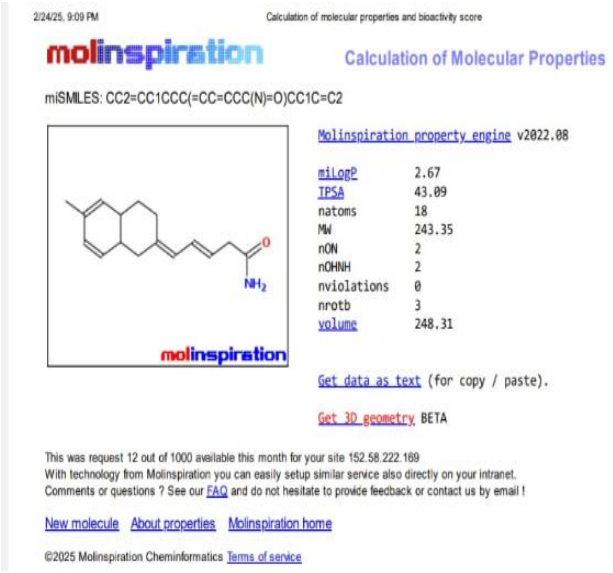
RXRA33	0.34	179.22	46.17	1	3	2	0
RXRA34	-0.76	216.26	89.26	3	5	2	0
RXRA35	-0.13	152.20	55.12	3	3	1	0
RXRA36	0.04	196.21	81.43	3	5	3	0
RXRA37	1.04	209.25	55.40	1	4	4	0
RXRA38	0.62	165.19	46.17	1	3	2	0
RXRA39	0.31	195.22	66.40	2	4	3	0
RXRA40	-0.40	166.22	55.12	3	3	2	0
RXRA41	1.79	234.29	54.37	1	3	2	0
RXRA42	2.24	264.32	74.60	2	4	3	0
RXRA43	1.39	299.39	97.46	3	5	3	0
RXRA44	2.85	233.35	43.09	2	2	2	0
RXRA45	0.88	298.41	103.26	4	5	3	0
RXRA46	2.85	233.35	43.09	2	2	2	0
RXRA47	3.54	247.38	43.09	2	2	3	0
RXRA48	1.28	233.31	60.16	2	3	2	0
RXRA49	1.44	299.39	97.46	3	5	3	0
RXRA50	0.99	269.37	77.24	2	4	2	0
RXRA51	4.88	403.52	69.55	3	4	6	0
RXRA52	5.15	392.97	38.05	3	2	5	1
RXRA53	4.90	457.04	72.19	3	4	6	0
RXRA54	6.91	429.60	38.33	1	3	8	1
RXRA55	6.44	399.58	21.26	1	2	7	1
RXRA56	6.19	441.62	38.33	1	3	8	1
RXRA57	6.29	399.58	29.10	1	2	6	1
RXRA58	6.26	407.99	21.26	1	2	6	1

RXRA59	3.91	438.59	92.42	4	5	6	0
RXRA60	5.17	448.99	72.19	3	4	7	1
RXRA61	-0.16	182.22	61.35	3	4	2	0
RXRA62	-1.73	182.18	78.42	3	5	2	0
RXRA63	-0.67	226.23	87.66	3	6	4	0
RXRA64	-2.65	246.29	127.31	6	7	3	1
RXRA65	-1.47	261.30	110.52	4	7	4	0
RXRA66	-2.13	247.28	121.52	5	7	3	0
RXRA67	-1.19	225.25	93.45	4	6	4	0
RXRA68	0.46	196.25	50.36	2	4	3	0
RXRA69	-0.99	210.23	78.42	5	3	3	0
RXRA70	-2.54	217.25	101.29	4	6	2	0
RXRA71	6.82	446.03	29.10	1	2	7	1
RXRA72	2.85	481.61	92.70	2	6	8	0
RXRA73	3.41	456.62	115.29	5	6	7	0
RXRA74	6.68	462.48	12.03	1	1	6	1
RXRA75	6.98	409.62	12.03	1	1	7	1
RXRA76	4.50	450.60	89.26	3	5	7	0
RXRA77	4.22	464.63	89.26	5	3	7	0
RXRA78	6.55	464.68	72.19	3	4	7	1
RXRA79	2.85	375.51	49.33	2	3	5	0
RXRA80	4.15	275.39	26.02	2	1	3	0
RXRA81	2.75	164.25	17.07	0	1	2	0
RXRA82	3.02	178.28	17.07	0	1	3	0
RXRA83	1.65	201.29	60.16	2	3	2	0
RXRA84	4.09	150.26	0.00	0	0	2	0

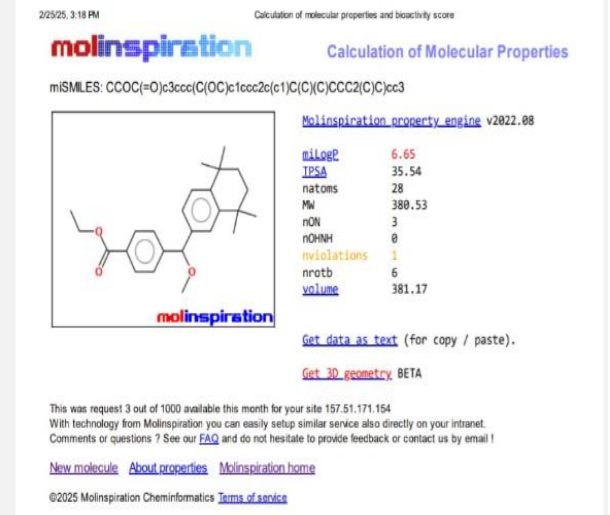
RXRA85	2.72	193.29	43.09	2	2	4	0
RXRA86	2.91	194.27	37.30	1	2	3	0
RXRA87	2.17	243.37	60.16	2	3	3	0
RXRA88	4.13	176.30	0.0	0	0	3	0
RXRA89	3.89	190.33	0.0	0	0	3	0
RXRA90	2.91	208.30	37.30	3	2	3	0
RXRA91	3.66	340.46	60.68	3	3	4	0
RXRA92	4.66	338.47	40.46	2	2	3	0
RXRA93	3.92	321.42	64.31	3	3	3	0
RXRA94	4.20	338.45	49.69	2	3	4	0
RXRA95	3.15	342.46	60.68	3	3	3	0
RXRA96	2.65	395.50	86.62	3	5	4	0
RXRA97	4.01	354.45	77.75	3	4	2	0
RxRA98	4.27	368.47	66.76	2	4	5	0
RXRA99	4.16	340.46	49.69	2	3	4	0
RXRA100	3.17	325.45	66.48	4	3	3	0

The physiochemical and biological properties of the best hits molecules were calculated, and their snapshots are given below.

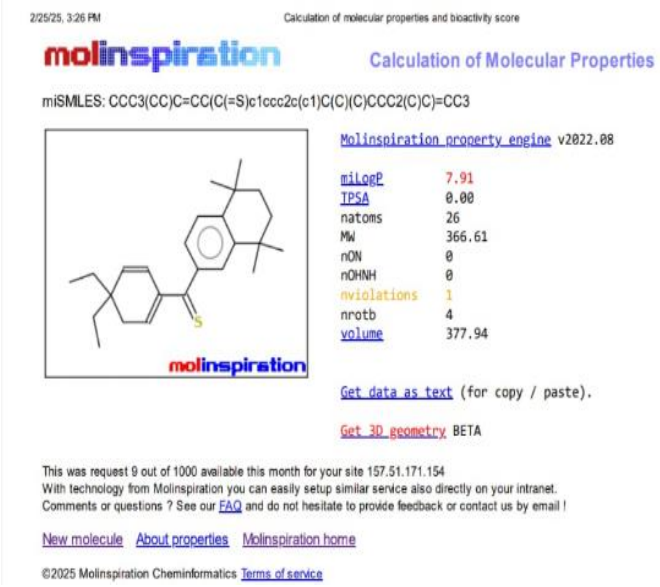
RXRA11



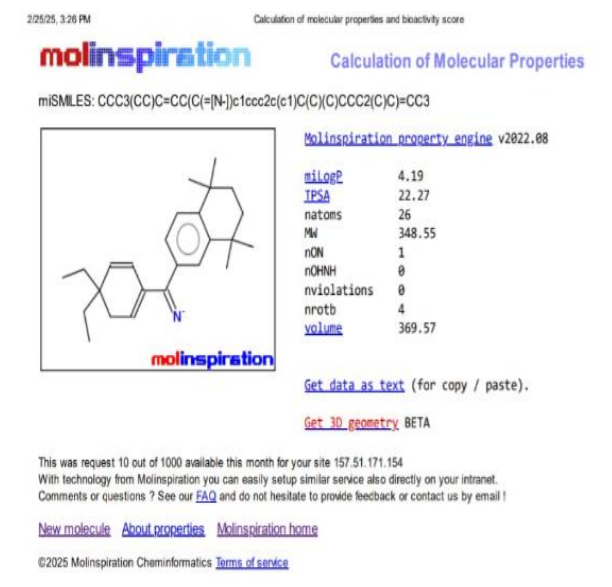
RXRA13



RXRA19



RXRA20



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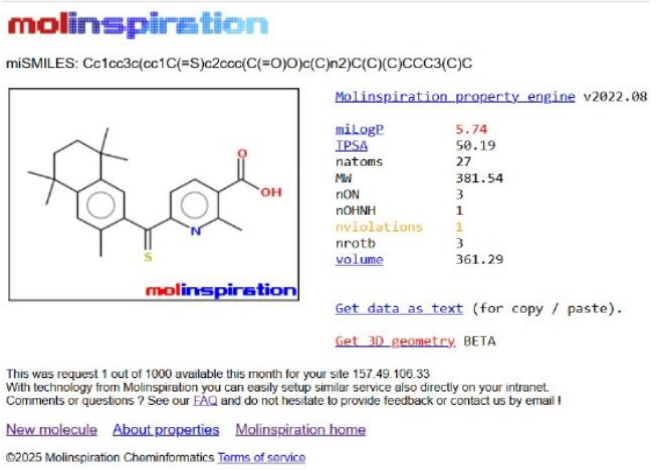

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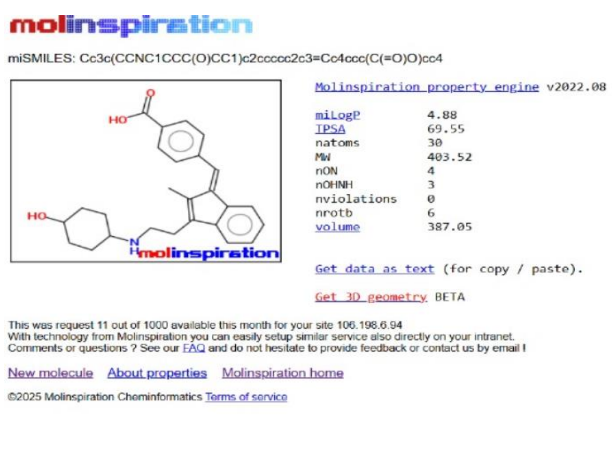

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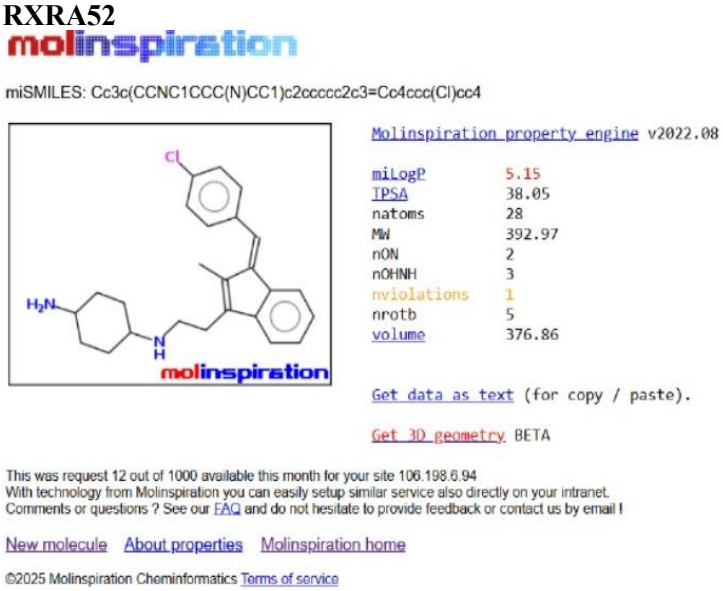
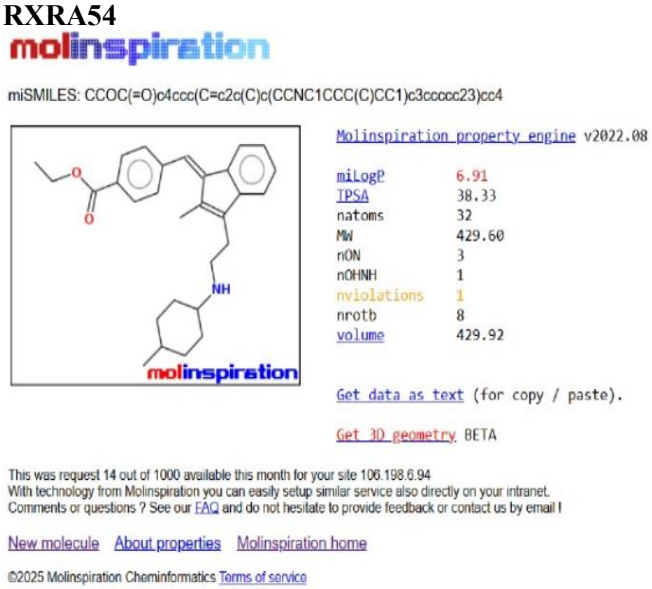


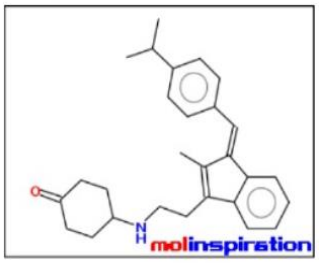
RXRA54



RXRA57

molinspiration

miSMILES: Cc3c(CCNC1CCC(=O)CC1)c2ccccc2c3=Cc4ccc(C(C)C)cc4



Molinspiration property engine v2022.08

miLogP	6.29
TPSA	29.10
natoms	30
MW	399.58
nON	2
nOHNH	1
nviolations	1
nrotb	6
volume	404.14

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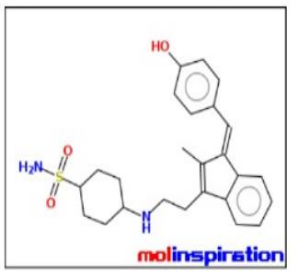
RXRA59

molinspiration

miSMILES: Cc3c(CCNC1CCC(S(N)(=O)=O)CC1)c2ccccc2c3=Cc4ccc(O)cc4



Molinspiration property engine v2022.08

miLogP	3.91
TPSA	92.42
natoms	31
MW	438.59
nON	5
nOHNH	4
nviolations	0
nrotb	6
volume	402.77

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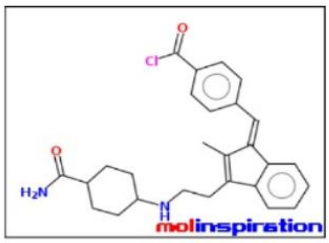
miSMILES: Cc3c(CCNC1CCC(C(N)=O)CC1)c2ccccc2c3=Cc4ccc(C(=O)Cl)cc4



Molinspiration property engine v2022.08

miLogP	5.17
TPSA	72.19
natoms	32
MW	448.99
nON	4
nOHNH	3
nviolations	1
nrotb	7
volume	414.82

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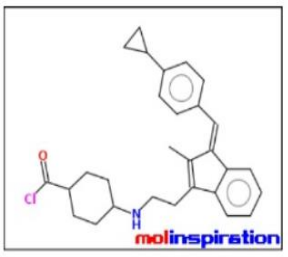
RXRA71

molinspiration

miSMILES: Cc3c(CCNC1CCC(C(=O)Cl)CC1)c2ccccc2c3=Cc5ccc(C4CC4)cc5



Molinspiration property engine v2022.08

miLogP	6.82
TPSA	29.10
natoms	32
MW	446.03
nON	2
nOHNH	1
nviolations	1
nrotb	7
volume	424.14

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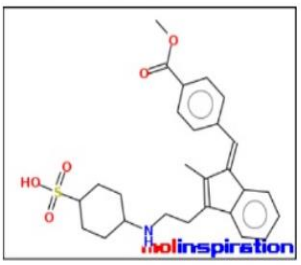
RXRA72

molinspiration

miSMILES: COC(=O)c4ccc(C=c2c(C)c(CCNC1CCC(S(=O)(=O)O)CC1)c3ccccc23)cc4



Molinspiration property engine v2022.08

miLogP	2.85
TPSA	92.70
natoms	34
MW	481.61
nON	6
nOHNH	2
nviolations	0
nrotb	8
volume	436.01

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RXRA76

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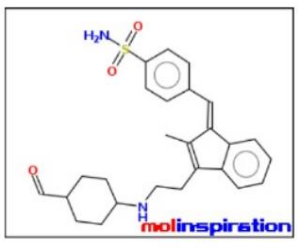
miSMILES: Cc3c(CCNC1CCC(C=O)CC1)c2ccccc2c3=Cc4ccc(S(N)(=O)=O)cc4



Molinspiration property engine v2022.08

miLogP	4.50
TPSA	89.26
natoms	32
MW	450.60
nON	5
nOHNH	3
nviolations	0
nrotb	7
volume	413.74

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RXRA77

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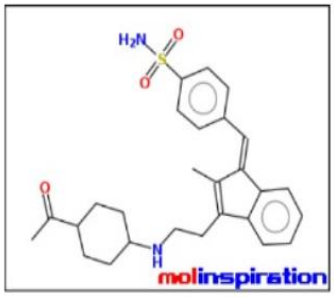
miSMILES: CC(=O)C4CCC(NCCc2c(C)c(=Cc1ccc(S(N)(=O)=O)cc1)c3ccccc23)CC4



Molinspiration property engine v2022.08

miLogP	4.22
TPSA	89.26
natoms	33
MW	464.63
nON	5
nOHNH	3
nviolations	0
nrotb	7
volume	430.30

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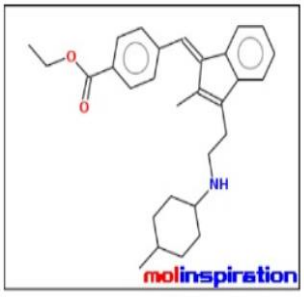
RXRA79

molinspiration

miSMILES: CCOC(=O)c4ccc(C=c2c(C)c(CCNC1CCC(C)CC1)c3ccccc23)cc4



Molinspiration property engine v2022.08

miLogP	6.91
TPSA	38.33
natoms	32
MW	429.60
nON	3
nOHNH	1
nviolations	1
nrotb	8
volume	429.92

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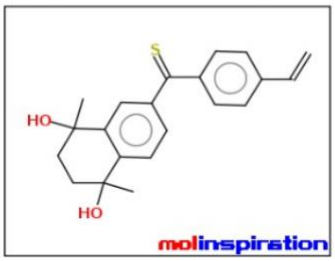
RXRA92

molinspiration

miSMILES: C=Cc3ccc(C(=S)c1ccc2c(c1)C(C)(O)CCC2(C)O)cc3



Molinspiration property engine v2022.08

miLogP	4.66
TPSA	40.46
natoms	24
MW	338.47
nON	2
nOHNH	2
nviolations	0
nrotb	3
volume	315.97

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New molecule About properties Molinspiration home

RXRA93

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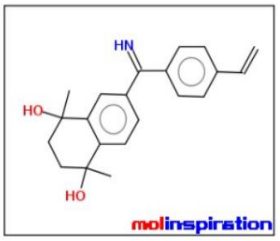
miSMILES: C=Cc3ccc(C(=N)c1ccc2c(c1)C(C)(O)CCC2(C)O)cc3



Molinspiration property engine v2022.08

miLogP	3.92
TPSA	64.31
natoms	24
MW	321.42
nON	3
nOHNH	3
nviolations	0
nrotb	3
volume	310.41

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RXRA95

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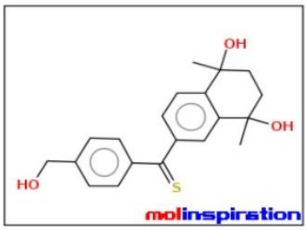
miSMILES: CC3(O)CCC(C)(O)c2cc(C(=S)c1ccc(CO)cc1)ccc23



Molinspiration property engine v2022.08

miLogP	3.15
TPSA	60.68
natoms	24
MW	342.46
nON	3
nOHNH	3
nviolations	0
nrotb	3
volume	313.06

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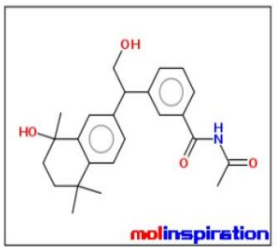
RXRA96

molinspiration

miSMILES: CC(=O)NC(=O)c3cccc(C(CO)c1ccc2c(c1)C(C)(O)CCC2(C)C)c3



Molinspiration property engine v2022.08

miLogP	2.65
TPSA	86.62
natoms	29
MW	395.50
nON	5
nOHNH	3
nviolations	0
nrotb	4
volume	377.50

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Get 3D geometry BETA

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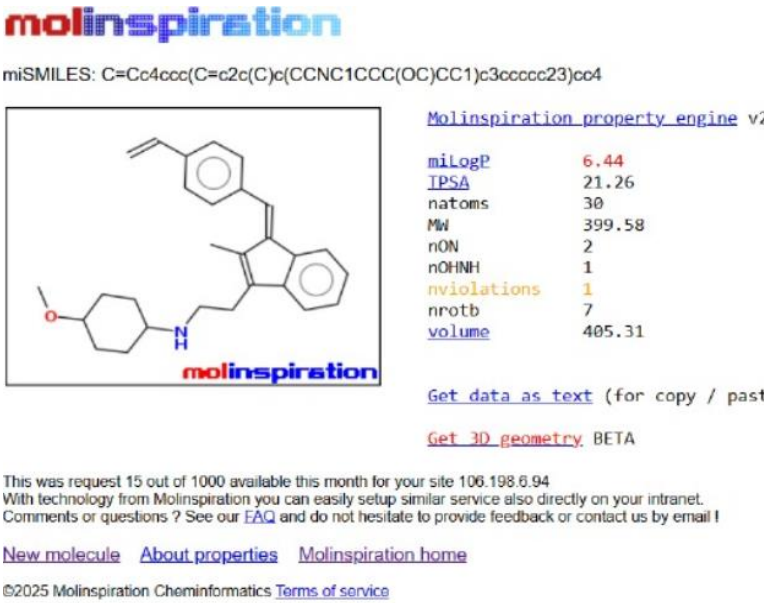
New molecule About properties Molinspiration home

RXRA55



ADMET properties: ADMETlab 2.0

ADMET Evaluation function module is composed of a series of high-quality prediction models trained by multi-task graph attention framework. It enables the users to conveniently and efficiently implement the calculation and prediction of 17 physicochemical properties, 13 medicinal chemistry measures, 23 ADME endpoints, and 27 toxicity endpoints and 8 toxicophore rules (751 substructures), thereby selecting promising lead compounds for further exploration. Detailed explanation and optimal range of each property are provided to help the users to get a whole ADMET picture of input molecule. The empirical-based decision states of each property are visually represented with different colored dots (green: excellent; yellow: medium; red: poor) [11-13].

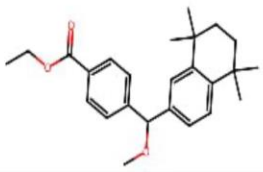
Table 4: Toxicity testing.

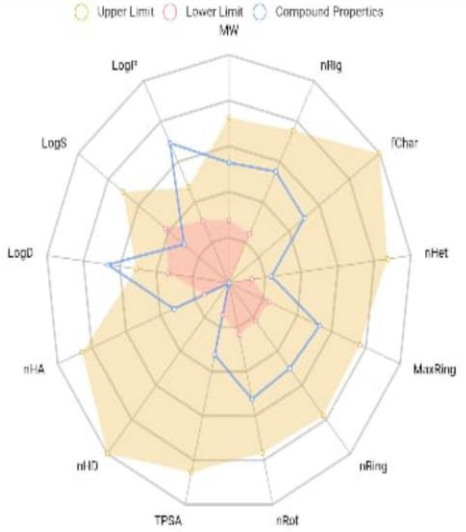
***In silico* Toxicity Explorer**	
Nontoxic Compound	**Toxic Compound**
RXRA1,RXRA2,RXRA3,RXRA4,RXRA5,RXRA 6,RXRA7,RXRA8,RXRA9,RXRA10, RXRA21, RXRA22, RXRA23, RXRA24, RXRA25, RXRA26, RXRA27, RXRA28, RXRA29,RXRA30,RXRA52,RXRA53,RXRA54,R XRA55,RXRA56,RXRA57,RXRA58,RXRA60,RX RA63,RXRA64,RXRA65,RXRA67,RXRA69,RXR A72,RXRA73,RXRA74,RXRA75,RXRA76,RXRA 77,RXRA78,RXRA80,RXRA89,RXRA91,RXRA9 2,RXRA93,RXRA94,RXRA95,RXRA96,RXRA97, RXRA98,RXRA99,RXRA100	RXRA11,RXRA12,RXRA13,RXRA14,RXRA15, RXRA16,RXRA17,RXRA18,RXRA19,RXRA20, RXRA31, RXRA32, RXRA33, RXRA34, RXRA35, RXRA36, RXRA37, RXRA38,RXRA39,RXRA40,RXRA41,RXRA42, RXRA43,RXRA44,RXRA45,RXRA46,RXRA47, RXRA48,RXRA49,RXRA50,RXRA59,RXRA61, RXRA62,RXRA66,RXRA68RXRA70,RXRA71, RXRA79,RXRA81,RXRA82,RXRA83,RXRA84, RXRA85,RXRA86,RXRA87,RXRA88,RXRA90

The ADMET properties of 100 molecules were predicted and some of the best hit molecules screenshots are given below

RXRA13

Home / ADMET Evaluation / Evaluation Results





Physicochemical Property	
Molecular Weight (MW)	380.240
Volume	423.202
Density	0.898
nHA	3
nHD	0
nRot	6
nRing	3
MaxRing	10
nHet	3
fChar	0
nRig	18
Flexibility	0.333
Stereo Centers	1
TPSA	35.530
logS	-5.937
logP	6.933
logD	4.761

Medicinal Chemistry	
QED	0.602
SAscore	2.907
Fsp^3	0.480
MCE-18	70.757
NPscore	0.178
Lipinski Rule	Accepted
Pfizer Rule	Rejected
GSK Rule	Rejected
Golden Triangle	Accepted
PAINS	0 alert(s)
ALARM NMR Rule	0 alert(s)
BMS Rule	0 alert(s)
Chelator Rule	0 alert(s)

Absorption	
Caco-2 Permeability	-4.972
MDCK Permeability	1.1e-05
Pgp-inhibitor	+++
Pgp-substrate	---
HIA	---
$F_{20\%}$	---
$F_{30\%}$	--

Distribution	
PPB	99.516%
VD	2.124
BBB Penetration	---
Fu	1.413%

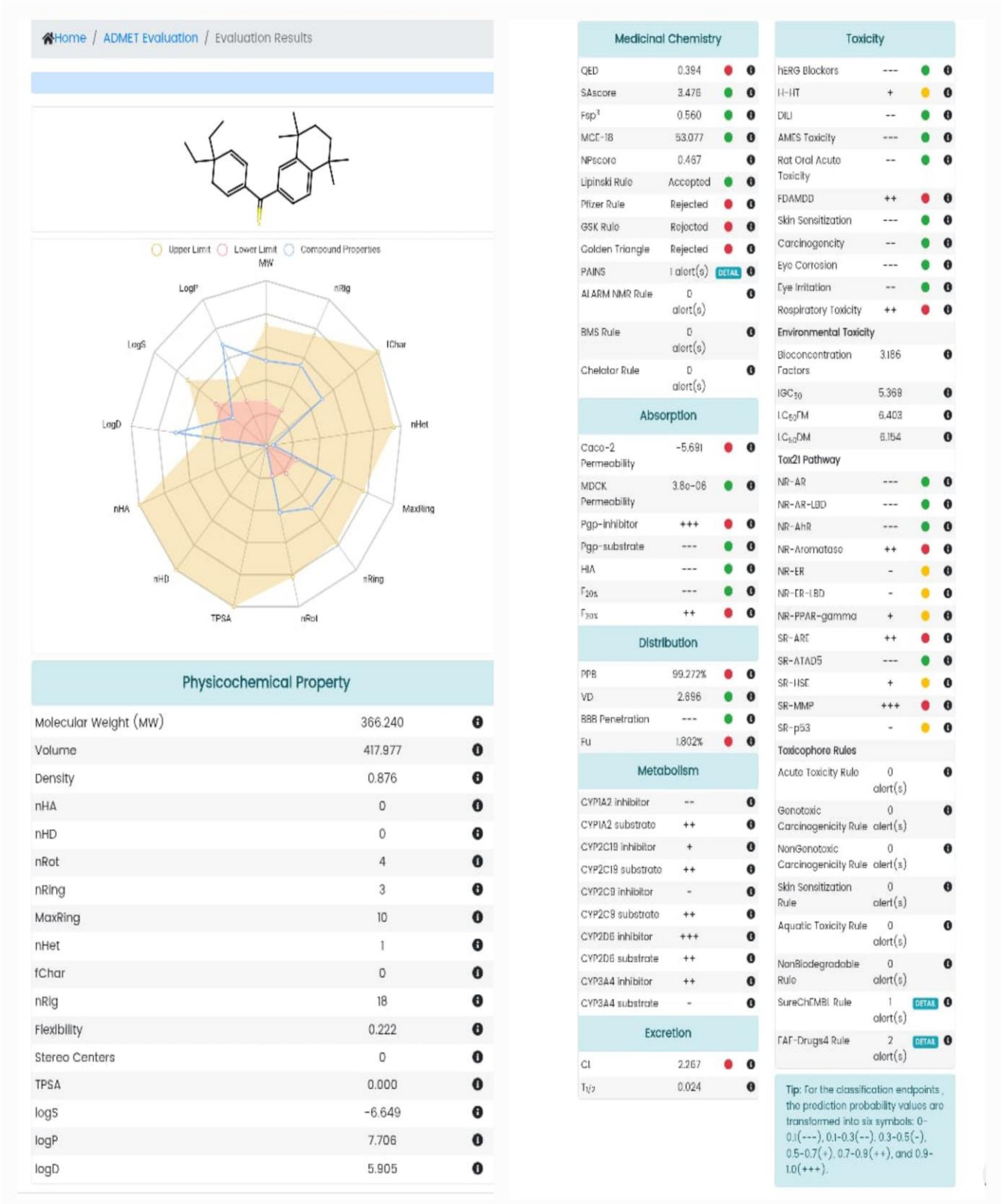
Metabolism	
CYP1A2 inhibitor	---
CYP1A2 substrate	+++
CYP2C19 inhibitor	+
CYP2C19 substrate	+
CYP2C9 inhibitor	-
CYP2C9 substrate	++
CYP2D6 inhibitor	+
CYP2D6 substrate	-
CYP3A4 inhibitor	-
CYP3A4 substrate	++

Excretion	
CL	3.729
$T_{1/2}$	0.014

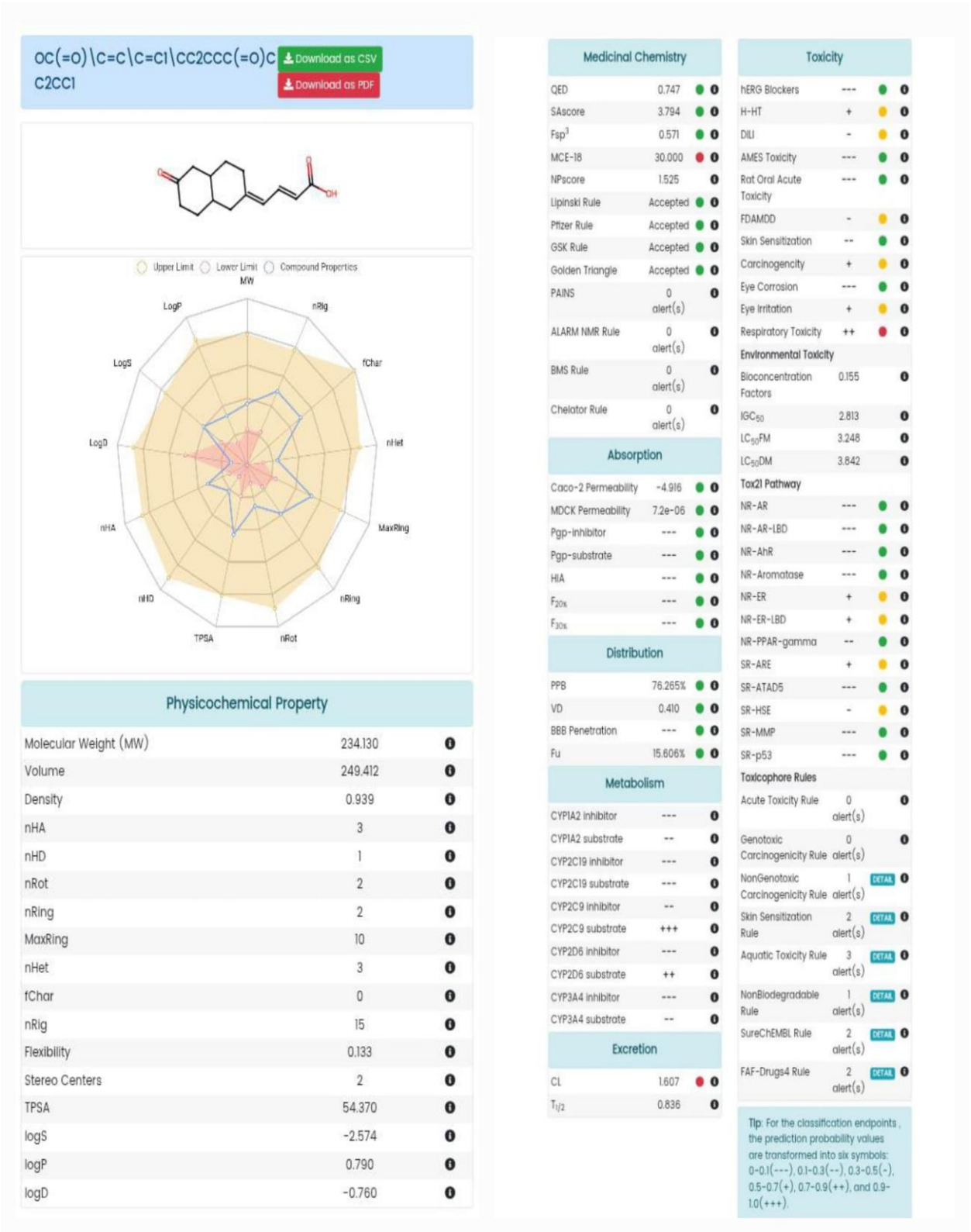
Toxicity		
hERG Blockers	-	
H-HT	---	
DILI	---	
AMES Toxicity	---	
Rat Oral Acute Toxicity	-	
FDAMDD	+++	
Skin Sensitization	--	
Carcinogencity	---	
Eye Corrosion	---	
Eye Irritation	+	
Respiratory Toxicity	-	
Environmental Toxicity		
Bioconcentration Factors	2.614	
IGC_{50}	5.334	
$LC_{50}FM$	6.115	
$LC_{50}DM$	6.684	
Tox21 Pathway		
NR-AR	---	
NR-AR-LBD	---	
NR-AhR	---	
NR-Aromatase	++	
NR-ER	++	
NR-ER-LBD	+++	
NR-PPAR-gamma	---	
SR-ARE	--	
SR-ATAD5	---	
SR-HSE	---	
SR-MMP	+++	
SR-p53	--	
Toxicophore Rules		
Acute Toxicity Rule	0 alert(s)	
Genotoxic Carcinogenicity Rule	0 alert(s)	
NonGenotoxic Carcinogenicity Rule	0 alert(s)	
Skin Sensitization Rule	0 alert(s)	
Aquatic Toxicity Rule	1 alert(s)	DETAIL
NonBiodegradable Rule	1 alert(s)	DETAIL
SureChEMBL Rule	0 alert(s)	
FAF-Drugs4 Rule	0 alert(s)	

Tip: For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

RXRA 19


Home / ADMET Evaluation / Evaluation Results
Upper Limit
Lower Limit
Compound Properties
MW
LogP
nRig
fChar
nHet
MaxRing
nRing
nRot
TPSA
nHD
nHA
LogD
LogS
Physicochemical Property
Molecular Weight (MW) 366.240
Volume 417.977
Density 0.876
nHA 0
nHD 0
nRot 4
nRing 3
MaxRing 10
nHet 1
fChar 0
nRig 18
Flexibility 0.222
Stereo Centers 0
TPSA 0.000
logS -6.649
logP 7.706
logD 5.905
Medicinal Chemistry
QED 0.394
SAscore 3.476
Fsp3 0.560
MCE-18 53.077
NPscore 0.467
Lipinski Rule Accepted
Pfizer Rule Rejected
GSK Rule Rejected
Golden Triangle Rejected
PAINS 1 alert(s) DETAIL
ALARM NMR Rule 0 alert(s)
BMS Rule 0 alert(s)
Chelator Rule 0 alert(s)
Absorption
Caco-2 Permeability -5.691
MDCK Permeability 3.8e-06
Pgp-inhibitor +++
Pgp-substrate ---
HIA ---
F20% ---
F30% ++
Distribution
PPB 99.272%
VD 2.696
BBB Penetration ---
Fu 1.802%
Metabolism
CYP1A2 inhibitor --
CYP1A2 substrate ++
CYP2C19 inhibitor +
CYP2C19 substrate ++
CYP2C9 inhibitor -
CYP2C9 substrate ++
CYP2D6 inhibitor +++
CYP2D6 substrate ++
CYP3A4 inhibitor ++
CYP3A4 substrate -
Excretion
CL 2.267
T1/2 0.024
Toxicity
hERG Blockers ---
H-HT +
DILI --
AMES Toxicity ---
Rat Oral Acute Toxicity --
FDAMDD ++
Skin Sensitization ---
Carcinogencity --
Eye Corrosion ---
Eye Irritation --
Respiratory Toxicity ++
Environmental Toxicity
Bioconcentration Factors 3.186
IGC50 5.369
LC50FM 6.403
LC50DM 8.154
Tox21 Pathway
NR-AR ---
NR-AR-LBD ---
NR-AhR ---
NR-Aromatase ++
NR-ER -
NR-ER-LBD -
NR-PPAR-gamma +
SR-ARE ++
SR-ATAD5 ---
SR-HSE +
SR-MMP +++
SR-p53 -
Toxicophore Rules
Acute Toxicity Rule 0 alert(s)
Genotoxic Carcinogenicity Rule 0 alert(s)
NonGenotoxic Carcinogenicity Rule 0 alert(s)
Skin Sensitization Rule 0 alert(s)
Aquatic Toxicity Rule 0 alert(s)
NonBiodegradable Rule 0 alert(s)
SureChEMBL Rule 1 alert(s) DETAIL
FAF-Drugs4 Rule 2 alert(s) DETAIL
Tip: For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

RXRA 41


OC(=O)\C=C\C=C1\CC2CCC(=O)C2CC1
Download as CSV
Download as PDF
Upper Limit
Lower Limit
Compound Properties
MW
nRig
fChar
nHet
MaxRing
nRing
nRot
TPSA
nHD
nHA
LogD
LogS
LogP
Physicochemical Property
Molecular Weight (MW) 234.130
Volume 249.412
Density 0.939
nHA 3
nHD 1
nRot 2
nRing 2
MaxRing 10
nHet 3
fChar 0
nRig 15
Flexibility 0.133
Stereo Centers 2
TPSA 54.370
logS -2.574
logP 0.790
logD -0.760
Medicinal Chemistry
QED 0.747
SAscore 3.794
Fsp3 0.571
MCE-18 30.000
NPscore 1.525
Lipinski Rule Accepted
Pfizer Rule Accepted
GSK Rule Accepted
Golden Triangle Accepted
PAINS 0 alert(s)
ALARM NMR Rule 0 alert(s)
BMS Rule 0 alert(s)
Chelator Rule 0 alert(s)
Absorption
Caco-2 Permeability -4.916
MDCK Permeability 7.2e-06
Pgp-inhibitor ---
Pgp-substrate ---
HIA ---
F20% ---
F30% ---
Distribution
PPB 76.265%
VD 0.410
BBB Penetration ---
Fu 15.606%
Metabolism
CYP1A2 inhibitor ---
CYP1A2 substrate --
CYP2C19 inhibitor ---
CYP2C19 substrate ---
CYP2C9 inhibitor --
CYP2C9 substrate +++
CYP2D6 inhibitor ---
CYP2D6 substrate ++
CYP3A4 inhibitor ---
CYP3A4 substrate --
Excretion
CL 1.607
T1/2 0.836
Toxicity
hERG Blockers ---
H-HT +
DILI -
AMES Toxicity ---
Rat Oral Acute Toxicity ---
FDAMDD -
Skin Sensitization --
Carcinogencity +
Eye Corrosion ---
Eye Irritation +
Respiratory Toxicity ++
Environmental Toxicity
Bioconcentration Factors 0.155
IGC50 2.813
LC50FM 3.248
LC50DM 3.842
Tox21 Pathway
NR-AR ---
NR-AR-LBD ---
NR-AhR ---
NR-Aromatase ---
NR-ER +
NR-ER-LBD +
NR-PPAR-gamma --
SR-ARE +
SR-ATAD5 ---
SR-HSE -
SR-MMP ---
SR-p53 ---
Toxicophore Rules
Acute Toxicity Rule 0 alert(s)
Genotoxic Carcinogenicity Rule 0 alert(s)
NonGenotoxic Carcinogenicity Rule 1 alert(s) DETAIL
Skin Sensitization Rule 2 alert(s) DETAIL
Aquatic Toxicity Rule 3 alert(s) DETAIL
NonBiodegradable Rule 1 alert(s) DETAIL
SureChEMBL Rule 2 alert(s) DETAIL
FAF-Drugs4 Rule 2 alert(s) DETAIL
Tip: For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

Molecular Docking

All the 100 newly designed ligands derived from the library are docked against the receptor protein RXRA using **SwissDock 2 (vina)** online platform. Results of predicted activity of all the designed ligands with fitness scores are tabulated below:

Table 5: Molecular docking studies.

S. No.	Ligand Code	Docking Score (kcal/mol)
1	RXRA1	-7.715
2	RXRA2	-7.927
3	RXRA3	-6.979
4	RXRA4	-7.691
5	RXRA5	-7.958
6	RXRA6	-8.419
7	RXRA7	-7.606
8	RXRA8	-7.459
9	RXRA9	-7.439
10	RXRA10	-8.36
11	RXRA11	-8.711
12	RXRA12	-6.411
13	RXRA13	-8.582
14	RXRA14	-6.166
15	RXRA15	-8.482
16	RXRA16	-8.497
17	RXRA17	-6.241
18	RXRA18	-6.021
19	RXRA19	-8.862
20	RXRA20	-8.616
21	RXRA21	-8.816
22	RXRA22	-7.46
23	RXRA23	-7.617
24	RXRA24	-7.817
25	RXRA25	-7.518
26	RXRA26	-7.893
27	RXRA27	-7.916
28	RXRA28	-7.549
29	RXRA29	-7.876
30	RXRA30	-7.894
31	RXRA31	-6.37
32	RXRA32	-6.184
33	RXRA33	-6.434
34	RXRA34	-6.826
35	RXRA35	-6.102
36	RXRA36	-6.594
37	RXRA37	-6.872
38	RXRA38	-6.28
39	RXRA39	-6.504
40	RXRA40	-6.326
41	RXRA41	-7.316
42	RXRA42	-7.617
43	RXRA43	-7.619
44	RXRA44	-7.937

45	RXRA45	-7.484
46	RXRA46	-7.627
47	RXRA47	-7.977
48	RXRA48	-7.526
49	RXRA49	-7.409
50	RXRA50	-7.034
51	RXRA51	-9.291
52	RXRA52	-9.381
53	RXRA53	-8.111
54	RXRA54	-9.136
55	RXRA55	-9.064
56	RXRA56	-8.461
57	RXRA57	-9.902
58	RXRA58	-7.595
59	RXRA59	-8.965
60	RXRA60	-9.065
61	RXRA61	-6.017
62	RXRA62	-5.473
63	RXRA63	-6.092
64	RXRA64	-6.416
65	RXRA65	-5.484
66	RXRA66	-6.657
67	RXRA67	-6.318
68	RXRA68	-5.726
69	RXRA69	-6.391
70	RXRA70	-5.239
71	RXRA71	-9.215
72	RXRA72	-8.559
73	RXRA73	-7.248
74	RXRA74	-8.014
75	RXRA75	-6.033
76	RXRA76	-8.664
77	RXRA77	-8.884
78	RXRA78	-7.029
79	RXRA79	-9.449
80	RXRA80	-8.249
81	RXRA81	-5.734
82	RXRA82	-6.565
83	RXRA83	-6.289
84	RXRA84	-6.506
85	RXRA85	-6.936
86	RXRA86	-6.317
87	RXRA87	-6.284
88	RXRA88	-6.642
89	RXRA89	-7.185
90	RXRA90	-4.937
91	RXRA91	-5.843
92	RXRA92	-9.128
93	RXRA93	-9.182
94	RXRA94	-7.729
95	RXRA95	-8.895
96	RXRA96	-8.73

97	RXRA97	-7.939
98	RXRA98	-7.714
99	RXRA99	-7.753
100	RXRA100	-7.074

Based on the docking score of all the 100 newly designed ligands, they are categorized and tabulated as follows.

Table 6: Classification based on docking score.

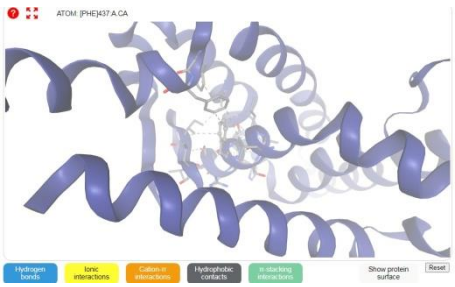
Highly Active	-8.5 to -10.0 kcal/mol
Moderately Active	-7.0 to -8.5 kcal/mol
Low Active	below -6 kcal/mol

Classification of designed ligands based on docking scores:

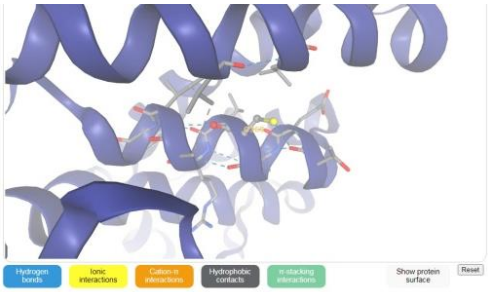
Table 7: Classification of new ligands based on docking scores.

HIGHLY ACTIVE (21)	MODERATELY ACTIVE (43)	LEAST ACTIVE (36)
RXRA57, RXRA79, RXRA52, RXRA51, RXRA71, RXRA93, RXRA54, RXRA92, RXRA60, RXRA55, RXRA59, RXRA95, RXRA77, RXRA19, RXRA21, RXRA96, RXRA11, RXRA76, RXRA20, RXRA13, RXRA72	RXRA16, RXRA15, RXRA56, RXRA6, RXRA10, RXRA80, RXRA53, RXRA74, RXRA47, RXRA5, RXRA97, RXRA44, RXRA2, RXRA27, RXRA30, RXRA26, RXRA29, RXRA24, RXRA99, RXRA94, RXRA1, RXRA98, RXRA4, RXRA46, RXRA43, RXRA23, RXRA42, RXRA7, RXRA58, RXRA28, RXRA48, RXRA25, RXRA45, RXRA22, RXRA8, RXRA9, RXRA49, RXRA41, RXRA73, RXRA89, RXRA100, RXRA50, RXRA78	RXRA3, RXRA85, RXRA37 RXRA34, RXRA66,RXRA88, RXRA36, RXRA82,RXRA84, RXRA39, RXRA33,RXRA64, RXRA12, RXRA69,RXRA31, RXRA40, RXRA67,RXRA86, RXRA83, RXRA87,RXRA38, RXRA17, RXRA32,RXRA14, RXRA35, RXRA63,RXRA75, RXRA18, RXRA61,RXRA91, RXRA81, RXRA68,RXRA65, RXRA62, RXRA70, RXRA90

On the basis of performed docking studies, 21 designed ligands are considered as best hit molecules [14-15], and their docking interaction snapshots are highlighted below.

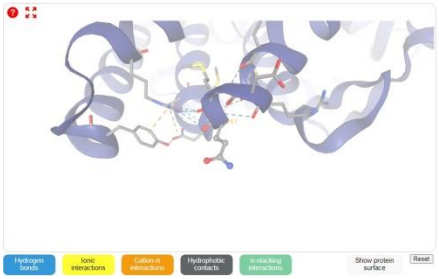


RXRA 51

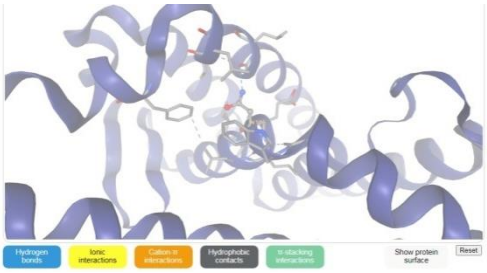


RXRA 52

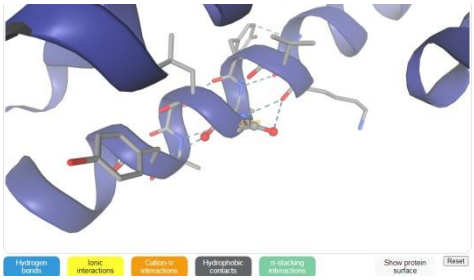
RXRA 54



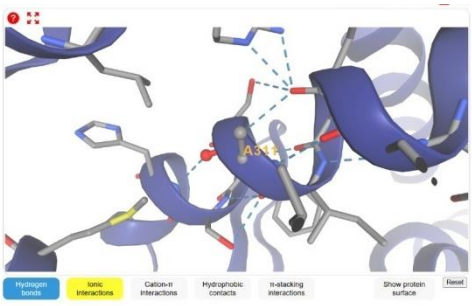
RXRA 55



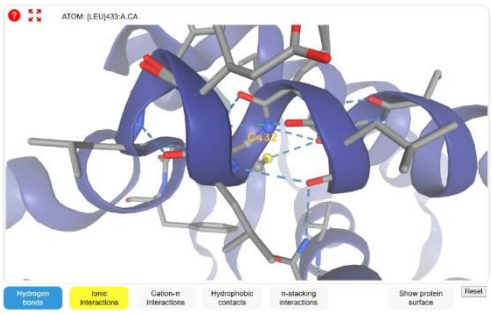
RXRA 57



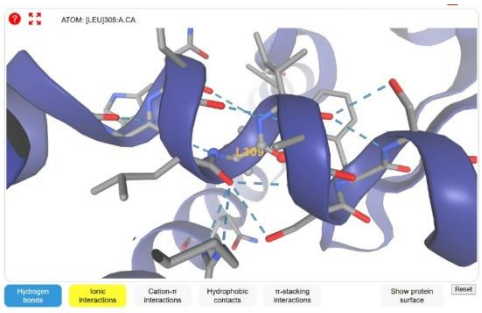
RXRA 59



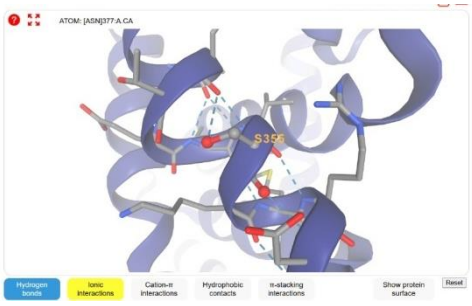
RXRA 21



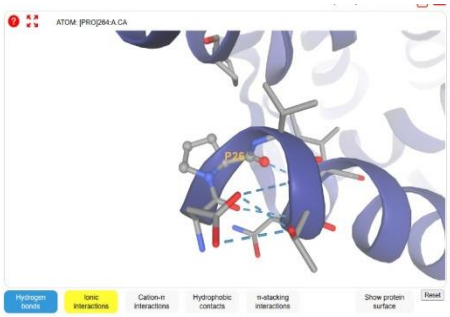
RXRA 71



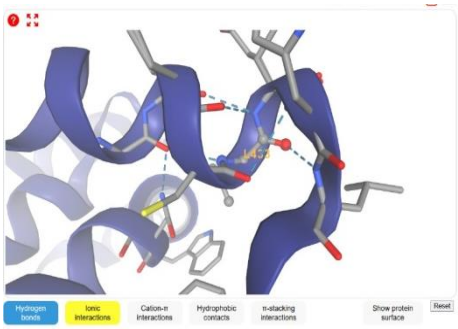
RXRA 72



RXRA 76



RXRA 77



RXRX 79

Conclusion

In silico identification approach has revealed newly designed novel RXRA (PDB ID: 4N8R) modulators that can be used in the treatment of PCOS. Based on the review of literature, the important structural features required for the modulation of RXRA were identified and the 3D structural query of novel 100 heterocyclic ligands were screened to retrieve new potent RXRA modulators. Drug likeliness of the newly designed compounds was studied with the help of Lipinski is rule of five and ADMET properties, which assisted us in screening of the non-drug like compounds. Later, the screened drug-like compounds were identified and further subjected to molecular docking study using SwissDock online platform creating a library of novel modulators of RXRA. Hence, we propose that the final hit compounds like hits RXRA57, RXRA52, RXRA93, RXRA54, RXRA92, RXRA60, RXRA55, RXRA95, RXRA77, RXRA21, RXRA96, RXRA76, and RXRA72 as possible virtual leads and are finally selected for synthesis. Out of 100 newly designed ligands, certain leads containing heterocyclic nucleus such o,o'-disubstituted biaryl cinnamic acid, benzoic acid with geminal biaryl ethenes can be synthesized and further evaluated for enzyme inhibitory assays, *in vitro* and *in vivo* PCOS treatment studies in future.

Author Contributions

All authors contributed equally to this research. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approvals

This study does not involve experiments on animals or human subjects.

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