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Research Article

VIRTUAL SCREENING STUDIES TO DESIGN DUAL INHIBITORS OF INTEGRASE AND CASPASE; QSAR, PHARMACOPHORE MODELING AND DOCKING STUDIES

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ABSTRACT

Objective: Resistance to antiretroviral drugs in current clinical practice is constantly increasing. Hence *denovo* design can provide better leads.

Methods: Novel Isatin sulfonamides derivatives that possess good activity against HIV-1 replication have been evaluated by QSAR, pharmacophore modelling and Docking Studies. 51 newly designed Isatin sulfonamide compounds have been designed by applying QSAR study. In order to see the activity, these compounds were docked with two proteins namely Integrase (3NF7) & Caspase (1NME).

Results & Conclusion: 10 compounds showed good activity with the proteins. The study minimizes the time and cost for finding the activity of compounds which will be useful for drug discovery and development. The results obtained reveal that some Isatin sulfonamide compounds exhibit anti HIV activity. QSAR and Pharmacophore Modelling study were carried out to find the best activity.

Keywords: Isatin sulfonamide, Denovo, QSAR, Docking Studies, Pharmacophore modeling,

INTRODUCTION

Isatin or 1H-indole-2, 3 –dione (Fig: a) was first obtained by Fegade JD[1] and Jain S K[2] in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. The compound is found in many plants. It is an endogenous compound identified in humans, and its effect has been studied in a variety of systems. It has aroused tremendous curiosity due to its diverse biological and pharmacological studies. Literature review represents some synthesized isatin derivatives and their pharmacological profiles with good activity which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines[3].

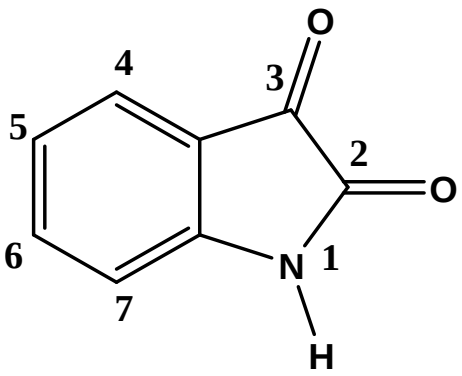


Fig. a

Sulphonamides are organosulfur compounds used against gram negative bacteria. The use of sulphonamides has been withdrawn due to bacterial resistance**.** The emergence of resistant bacterial strains replaced sulfonamides with other dihydrofolate reductase inhibitors. Certain deazapteridine derivatives have also been shown *in silico* to inhibit human dihydrofolate reductase[4]. Schiff's and N-Mannich bases of Isatin and its derivatives with Carbamimidoyl Benzene Sulfonamides were reported to exhibit anti bacterial activity against Gram positive and Gram negative strains[5]. Bis-Schiff bases of isatin and their derivatives were reported to possess least anti-bacterial, anti fungal and anti viral activity[6]. Mannich bases of N-methyl isatin-β-Thiosemicarbazone (MIBT) were found to inhibit Flaviviruses such as Japanese encephalitis virus and West nile virus replication[7]. Integrase is an enzyme that integrates HIV genetic material into the DNA of human CD4 cells making it possible for the infected cell to make new copies of HIV. Inhibition of integrase with tetracyclines has shown to possess anti-HIV and anti-mycobacterial activity[8].

MATERIALS AND METHODS

The drug discovery and development process has become more quantitative and much more computational in recent years.

In this study QSAR was chosen for structure activity relationship, Pharmacophore Modeling for generating hypothesis and finally Docking Studies to know the binding affinity of proteins with the drugs were carried out.

The QSAR study was done in CERIUS 2 software, Pharmacophore Modeling was studied in CATALYST and Docking studies were carried out in GLIDE licensed by SCHRODINGER software. Isatin Sulfonamide derivatives were taken for the study to estimate the activity of these derivatives which will be beneficial for the treatment of HIV.

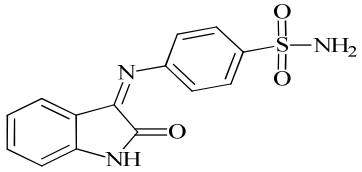
The standard Isatin Sulfonamide derivatives along with the activity were provided by GVK Bioscience. Among the various derivatives provided 45 compounds were taken for study. These compounds were divided into training set and test set. The descriptors were added simultaneously and alignment of molecules was done. Pharmacophore Modeling was done to identify new leads. It was studied by using CATALYST, one of the leading software products for Pharmacophore modeling and 3D-database searching. 41 various Isatin sulfonamide derivatives were provided by GVK Bioscience. These compounds were divided into training set and test set and a hypothesis model was generated.

Newly designed compounds were drawn according to the results of Predicted activity. These compounds were shown in **Table 1.**

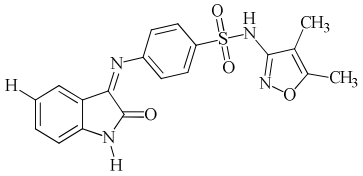
RESULTS AND DISCUSSION

These newly designed compounds were studied by using GFA method and QSAR was carried out. From the study, activity was estimated for the newly designed compounds. These compounds were compared with the predicted activity of standard compounds and finally from the comparison the best activity compounds were selected for DOCKING study. The selected compounds are listed in **Table 2.**

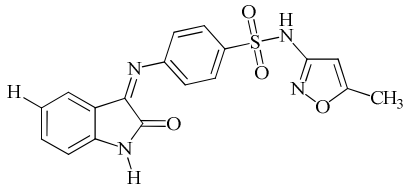
Table 1: Newly designed compounds



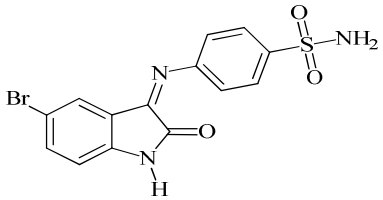
Compound 1a
M.F : $C_{14}H_{11}N_3O_3S$
M.W: 301.32



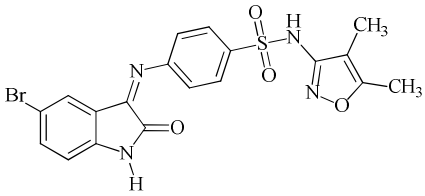
Compound 1b
M.F: $C_{19}H_{16}N_4O_4S$
M.W: 396.419



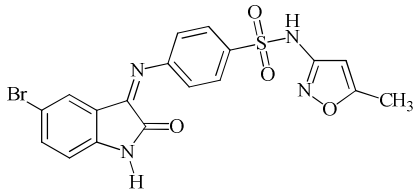
Compound 1c
M.F: $C_{18}H_{14}N_4O_4S$
M.W: 382.393



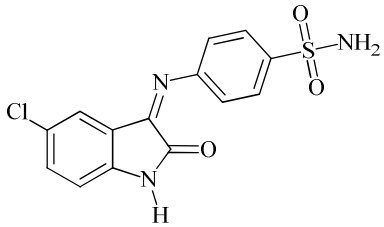
Compound 2a
M.F : $C_{14}H_{10}BrN_3O_3S$
M.W: 380.217



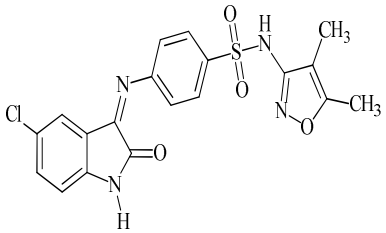
Compound 2b
M.F: $C_{19}H_{15}BrN$
M.W: 475.31



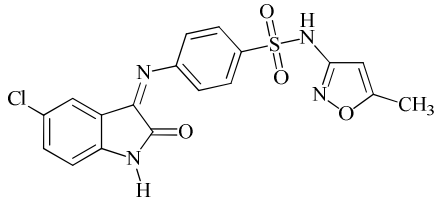
Compound 2c
M.F: $C_{18}H_{13}BrN_4O_4S$
M.W: 461.289



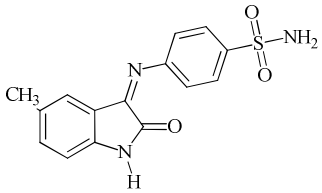
Compound 3a
M.F: $C_{14}H_{10}ClN_3O_3S$
M.W: 335.766



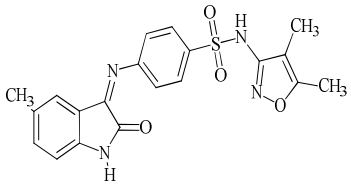
Compound 3b
M.F: $C_{19}H_{15}ClN_4O_4S$
M.W: 430.865



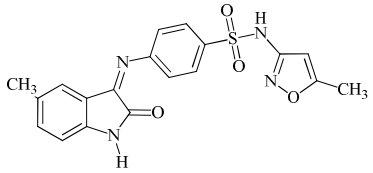
Compound 3c
M.F: $C_{18}H_{13}ClN_4O_4S$
M.W: 416.832



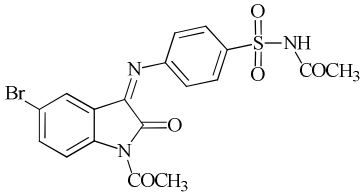
Compound 4a
M.F: $C_{15}H_{13}N_3O_3S$
M.W: 315.347



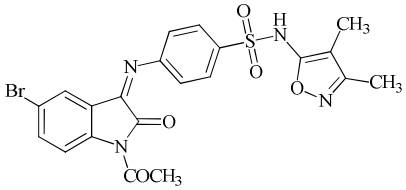
Compound 4b
M.F: $C_{20}H_{18}N_4O_4S$
M.W: 410.446



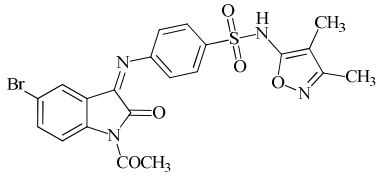
Compound 4c
M.F: $C_{19}H_{16}N_4O_4S$
M.W: 396.425



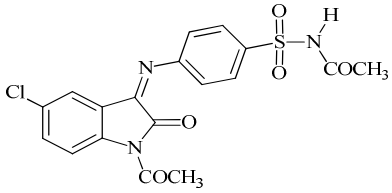
Compound 5a
M.F: $C_{18}H_{14}BrN_3O_5S$
M.W: 464.289



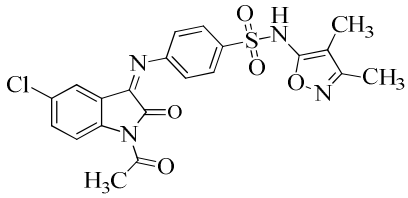
Compound 5b
M.F: $C_{21}H_{17}BrN_4O_5S$
M.W: 517.352



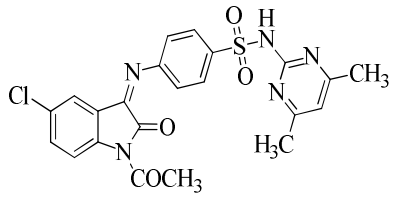
Compound 5c
M.F: $C_{22}H_{18}BrN_5O_4S$
M.W: 528.378



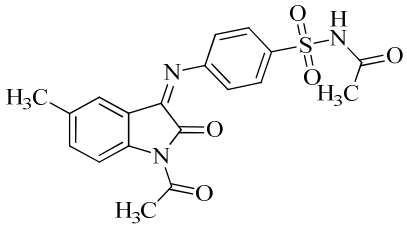
Compound 6a
M.F: $C_{18}H_{14}ClN_3O_5S$
M.W: 419.839



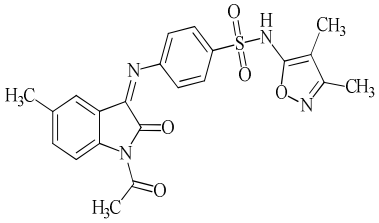
Compound 6b
M.F: $C_{21}H_{17}ClN_4O_5S$
M.W: 472.901



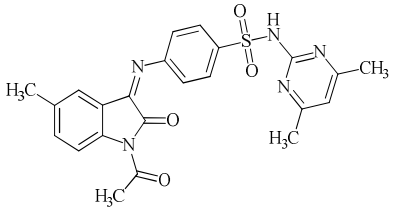
Compound 6c
M.F: $C_{22}H_{18}ClN_5O_4S$
M.W: 483.927



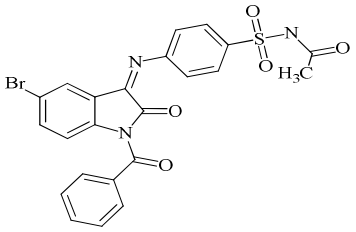
Compound 7a
M.F: $C_{19}H_{17}N_3O_5S$
M.W: 399.088



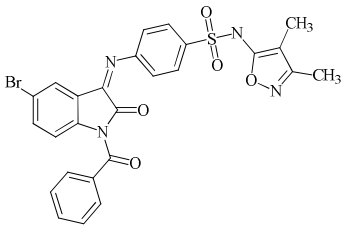
Compound 7b
M.F: $C_{22}H_{20}N_4O_5S$
M.W: 452.483



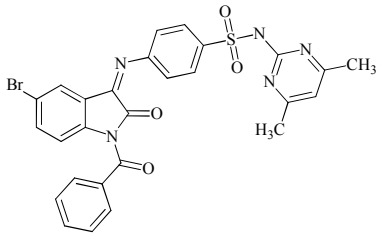
Compound 7c
M.F: $C_{23}H_{21}N_5O_4S$
M.W: 463.509



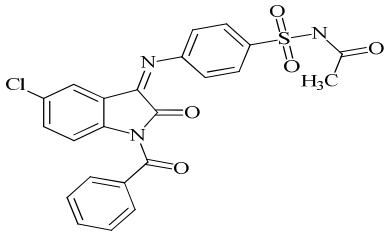
Compound 8a
M.F: $C_{23}H_{16}BrN_3O_5S$
M.W: 526.367



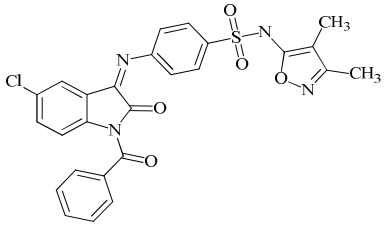
Compound 8b
M.F: $C_{26}H_{19}BrN_4O_5S$
M.W: 579.422



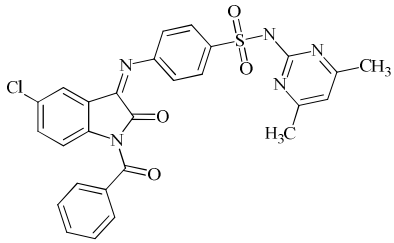
Compound 8c
M.F: $C_{27}H_{20}BrN_5O_4S$
M.W: 590.448



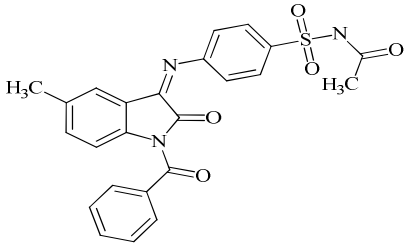
Compound 9a
M.F: $C_{23}H_{16}ClN_3O_5S$
M.W: 481.908



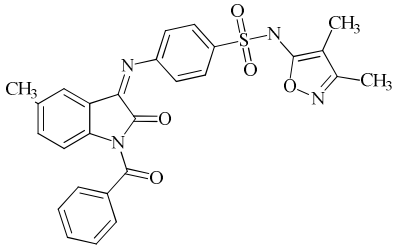
Compound 9b
M.F: $C_{26}H_{19}ClN_4O_5S$
M.W: 534.971



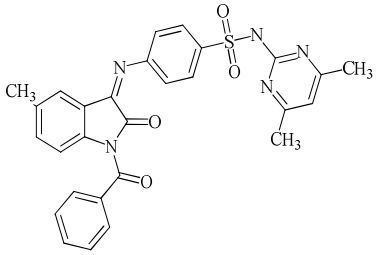
Compound 9c
M.F: $C_{27}H_{20}ClN_5O_4S$
M.W: 545.997



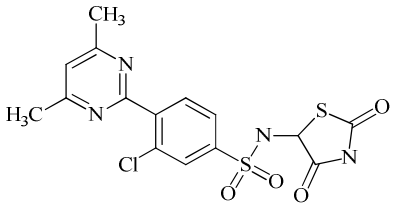
Compound 10a
M.F: $C_{24}H_{19}N_3O_5S$
M.W: 461.489



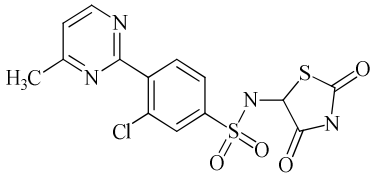
Compound 10b
M.F: $C_{27}H_{22}N_4O_5S$
M.W: 514.553



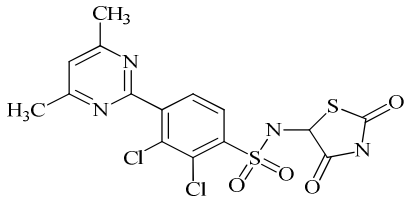
Compound 10c
M.F: $C_{28}H_{23}N_5O_4S$
M.W: 525.578



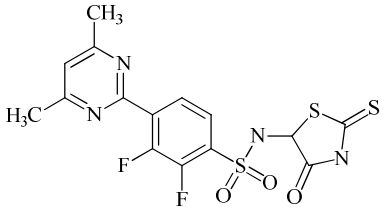
Compound 11a
M.F: $C_{15}H_{13}ClN_4O_4S$
M.W: 412.007



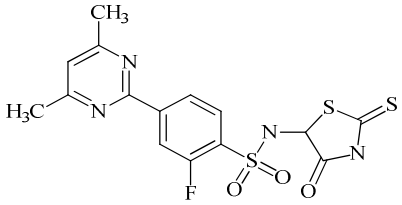
Compound 11b
M.F: $C_{14}H_{11}ClN_4O_4S_2$
M.W: 398.845



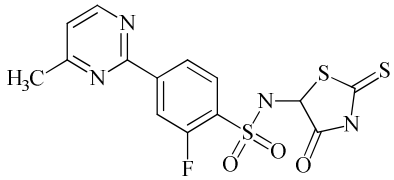
Compound 11c
M.F: $C_{15}H_{12}Cl_2N_4O_4S_2$
M.W: 447.316



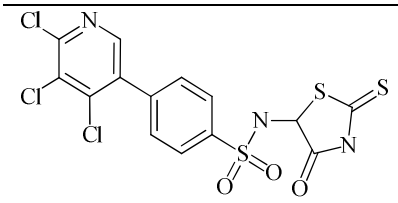
Compound 12a
M.F: $C_{15}H_{12}F_2N_4O_3S_3$
M.W: 430.476



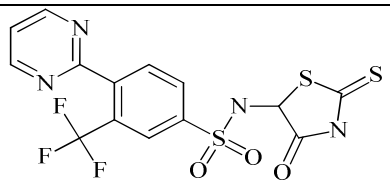
Compound 12b
M.F: $C_{15}H_{13}FN_4O_3S_3$
M.W: 412.482



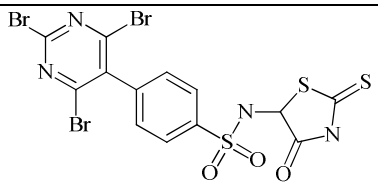
Compound 12c
M.F: $C_{14}H_{11}FN_4O_3S_3$
M.W: 397.455



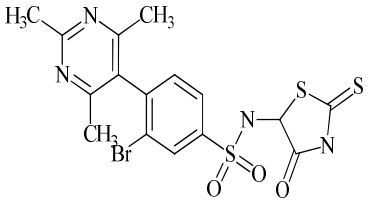
Compound 13a
M.F: $C_{14}H_8Cl_3N_3O_3S_3$
M.W: 468.786



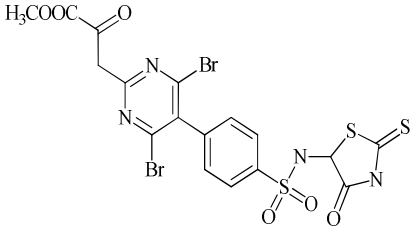
Compound 13b
M.F: $C_{14}H_9F_3N_4O_3S_3$
M.W: 434.436



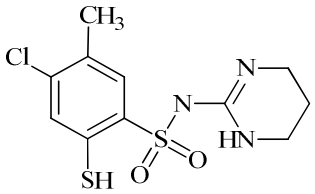
Compound 13c
M.F: $C_{13}H_7Br_3N_4O_3S_3$
M.W: 603.127



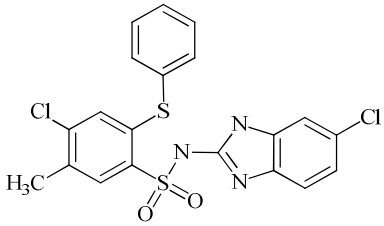
Compound 14a
M.F: $C_{16}H_{15}BrN_4O_3S_3$
M.W: 487.414



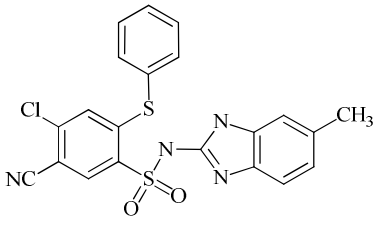
Compound 14b
M.F: $C_{17}H_{12}Br_2N_4O_6S_3$
M.W: 621.83



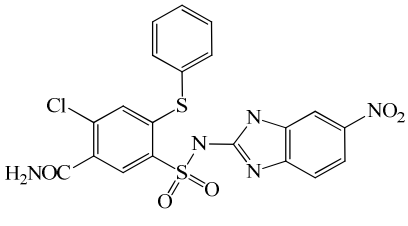
Compound 14c
M.F: $C_{11}H_{14}ClN_3O_2S_2$
M.W: 319.835



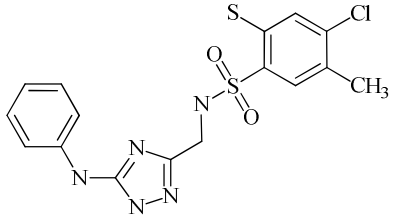
Compound 15a
M.F: $C_{20}H_{15}Cl_2N_3O_2S_2$
M.W: 464.389



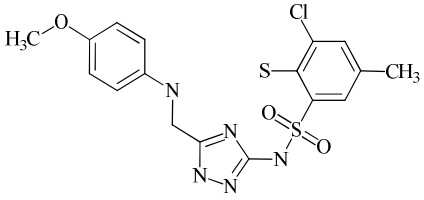
Compound 15b
M.F: $C_{21}H_{15}ClN_4O_2S_2$
M.W: 454.952



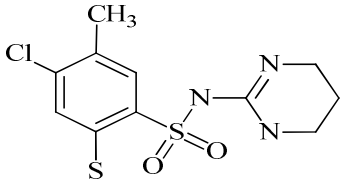
Compound 15c
M.F: $C_{20}H_{14}ClN_5O_5S_2$
M.W: 503.94



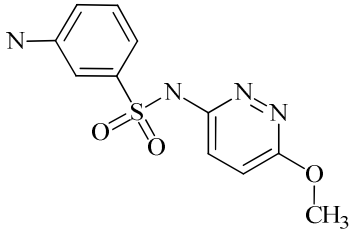
Compound 16a
M.F: $C_{16}H_{16}ClN_5O_2S_2$



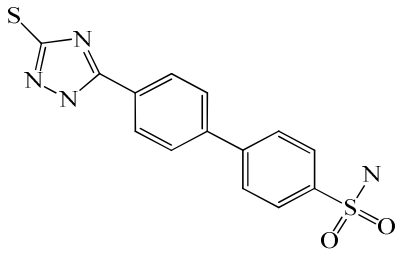
Compound 16b
M.F: $C_{17}H_{18}ClN_5O_3S_2$



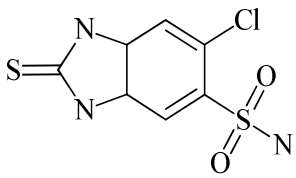
Compound 16c
M.F: $C_{11}H_{14}ClN_3O_2S_2$



Compound 17a
M.F: $C_{11}H_{12}N_4O_3S$
M.W: 280.309



Compound 17b
M.F: $C_{14}H_{12}N_4O_2S_2$
M.W: 332.04



Compound 17c
M.F: $C_7H_8ClN_3O_2S_2$
M.W: 265.740

Table 2: Cat Study Table: Activity Data

S. No.	Structure Name	Activity	Uncertainity
1.	Cat Compound_1	30.00	3
2.	Cat Compound_4	57.00	3
3.	Cat Compound_7	11.00	3
4.	Cat Compound_8	28.00	3
5.	Cat Compound_14	0.52	3
6.	Cat Compound_16	392.00	3
7.	Cat Compound_28	100.00	3
8.	Cat Compound_36	57.00	3

The test set compounds were generated and the best 11 hypo model was created. The results were tabulated in **Table 3.** Among the 11 hypo model the best hypo value was chosen for the study. From the hypothesis of these test compounds TRAINING HYPO 4330.4 showed good hypo value and this hypothesis and pharmacophore pattern was used for estimating the activity for the test compounds. The results are tabulated in **Table 4.**

Table 3: Test set compounds Output Test Hypo-4330

S. No.	Hypothesis	Hypo Value
1.	Training Hypo 4330.0	-
2.	Training Hypo 4330.1	-
3.	Training Hypo 4330.2	0.984025
4.	Training Hypo 4330.3	0.981736
5.	Training Hypo 4330.4	0.987484
6.	Training Hypo 4330.5	0.978299
7.	Training Hypo 4330.6	0.975929
8.	Training Hypo 4330.7	0.979388
9.	Training Hypo 4330.8	0.970497
10.	Training Hypo 4330.9	0.969173
11.	Training Hypo 4330.10	0.967056

Table 4: Test set – Output Hypo 4330.4

S. No.	Compounds	Activity	Estimated Activity	Fitness	Conformational Energy
1.	Compound 2	30	32	6.87647	9.9841
2.	Compound 4	57	51	6.66888	2.31932
3.	Compound 7	11	23	7.01594	1.73965
4.	Compound 8	28	28	6.9401	1.09139
5.	Compound 14	0.52	0.63	8.5785	7.06646
6.	Compound 16	392	230	8.5785	7.06646
7.	Compound 28	100	90	6.42575	3.88779
8.	Compound 36	57	53	6.65527	13.6826

The training set compounds were generated and the best 11 hypo model was created. Among the 11 hypo models the best hypo value was chosen for the study. From the hypothesis of these test compounds TRAINING HYPO 20.4 showed good hypo value and this hypothesis and pharmacophore pattern was used for estimating the activity of the training compounds. 20 compounds showed good activity.

Among the 20 compounds 10 best compounds were selected for further hypothesis generation. The newly designed compounds which were drawn based upon the predicted activity results from QSAR study were taken. These 51 compounds were imported and output hypo 20.4 was applied to find out the activity of new compounds.

From both the results of QSAR and Pharmacophore Modelling 21 compounds were chosen best and these compounds were selected for Docking Study. These 21 compounds were listed and tabulated in **Table 5.**

Table 5: Final compounds

S. No.	Compounds	QSAR		CAT	
		GFA	GPLS	Hypo 20.4	Hypo 20.5
1.	Compound 1a	5.130	5.103	220	140
2.	Compound 3a	4.920	5.139	200	24
3.	Compound 4a	5.109	5.071	200	28
4.	Compound 4c	5.185	4.751	130	20
5.	Compound 5a	-	-	570	24
6.	Compound 6a	-	-	480	23
7.	Compound 7a	4.611	4.626	440	29
8.	Compound 7c	5.012	5.000	24	27
9.	Compound 8c	5.248	5.227	19	16
10.	Compound 9a	4.514	4.688	140	24
11.	Compound 9c	5.719	5.115	20	18
12.	Compound 10a	5.369	5.247	140	21
13.	Compound 11a	5.070	4.753	79	13
14.	Compound 11b	5.704	4.727	97	14
15.	Compound 12b	5.659	4.656	81	14
16.	Compound 12c	6.226	4.736	23	13
17.	Compound 13c	4.963	5.014	110	64
18.	Compound 14b	-	-	73	28
19.	Compound 16c	5.132	5.193	76	14
20.	Compound 17b	5.357	5.218	200	130
21.	Compound 17c	4.639	5.084	71	9.6

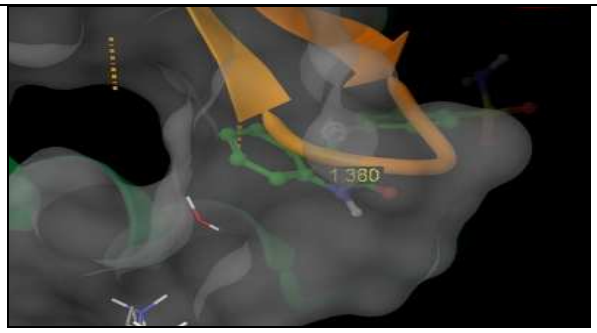
Docking study was carried out by using GLIDE software. The study illustrates docking on HIV inhibitors to the target protein. In this study two proteins (Integrase & Caspase) were taken for study. The protein was downloaded from PDB and protein preparation workflow was carried out. Each and every molecule of those selected 21 compounds was drawn and it was converted to MOL and 3D format by using Online SMILES translator.

Generation of GRID was done to dock the protein with the ligand (drug). Docking was carried out for both proteins (Integrase & Caspase).

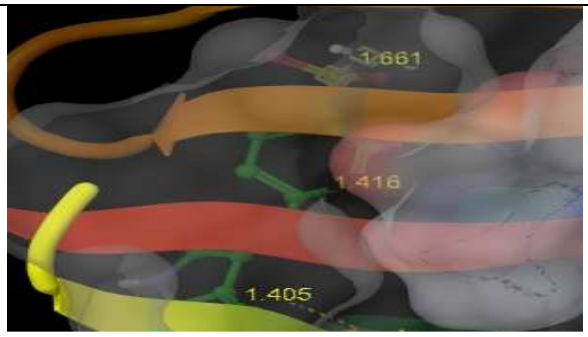
Finally from the results of both proteins the standard protein results were compared and among the 21 compounds 10 compounds posses best activity for both the proteins. The results were tabulated in **Table 6** .The activity data table was shown in **Figure c** . The proteins with the ligand docked are shown **Figure b.**These compounds may possess good activity which will be effective against HIV-1 replication.

Table 6: Best Activity Compounds from Both Proteins (3NF7 & 1NME)

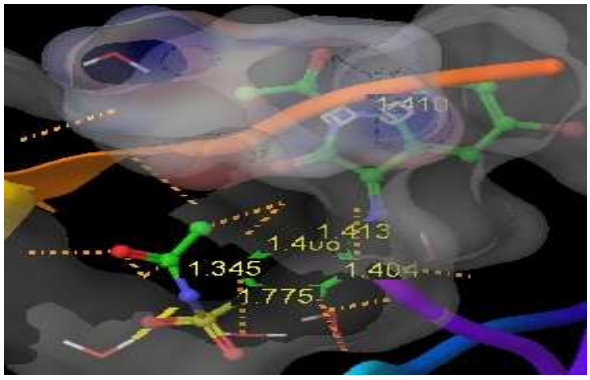
S. No.	Compounds	G Score		Ligand Activity
		3NF7 (-7.23)	1NME (-6.9)	
1.	1a	-5.06	-3.7	3NF7
2.	3a	-5.71	-3.35	3NF7
3.	5a	-4.79	-5.46	1NME
4.	7a	-4.82	-5.88	1NME
5.	11a	-5.54	-7.69	3NF7,1NME
6.	11b	-4.86	-8.14	1NME
7.	12c	-5.83	-4.64	3NF7
8.	13c	-5.76	-3.94	3NF7
9.	14b	-6.57	-5.01	3NF7,1NME
10.	16c	-5.81	-3.92	3NF7



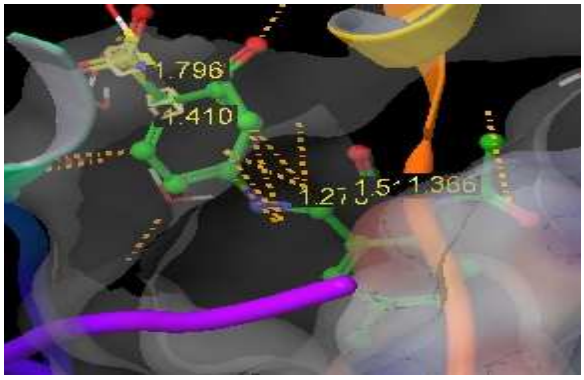
Compound 1a with 3NF7 protein



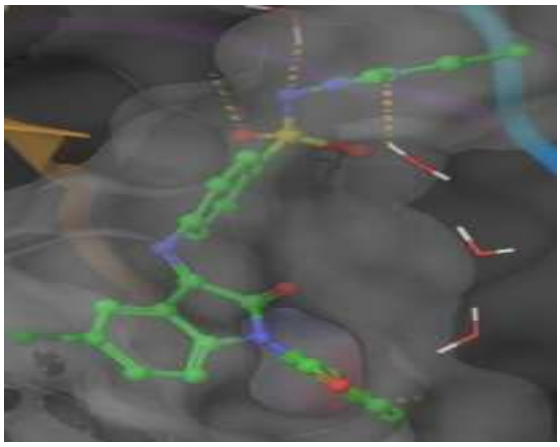
Compound 3a with 3NF7 protein



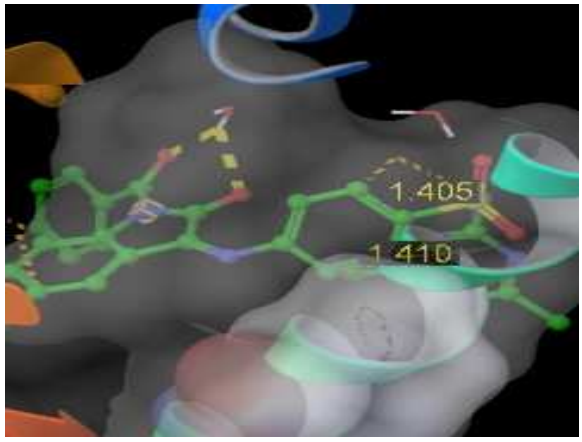
Compound 5a with 1NME



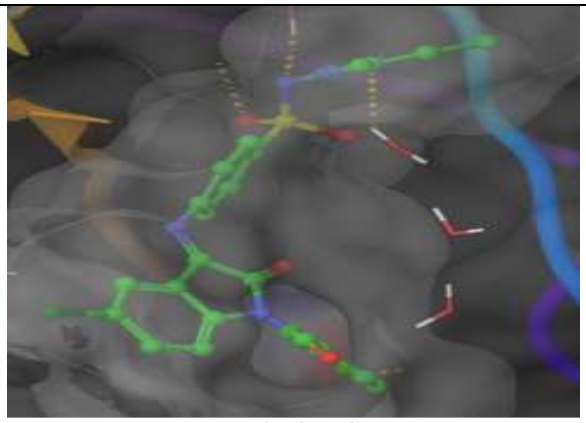
Compound 7a with 1NME



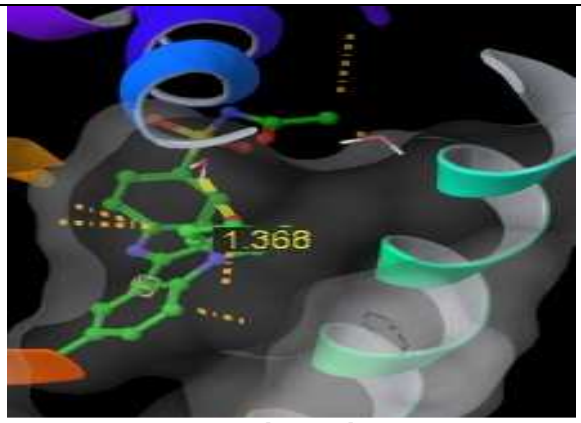
Compound 11a with 1NME



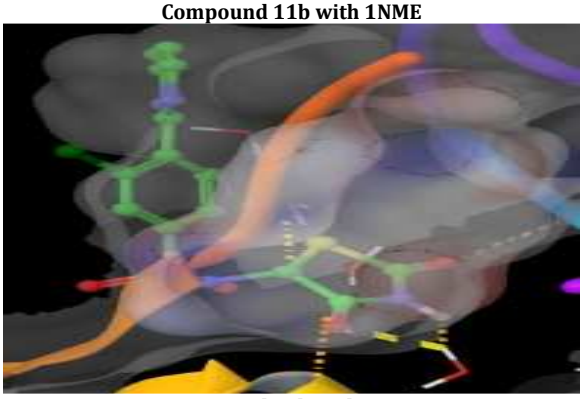
Compound 11a with 3NF7



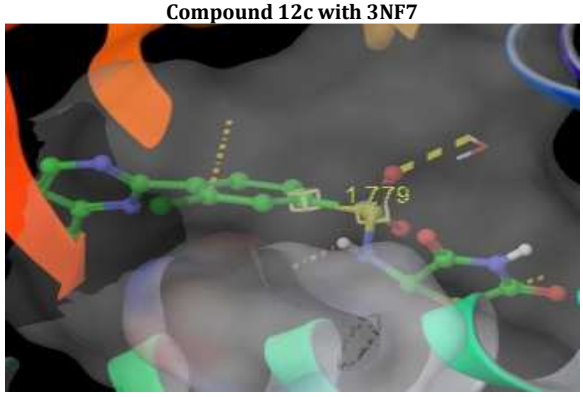
Compound 11b with 1NME



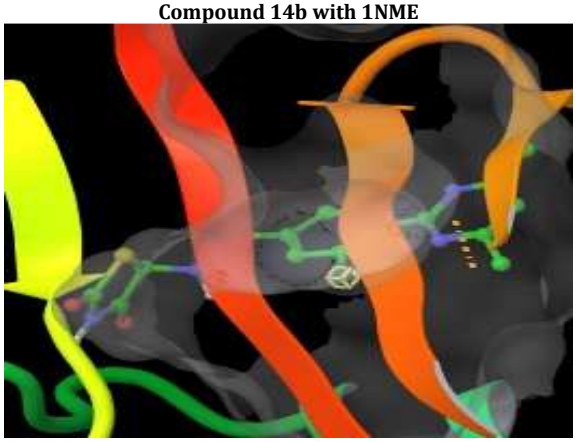
Compound 12c with 3NF7



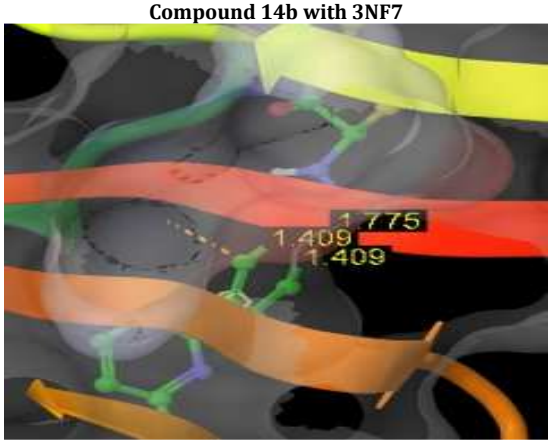
Compound 14b with 1NME



Compound 14b with 3NF7



Compound 13c with 3NF7



Compound 16c with 3NF7

Fig. b: Best docked compounds

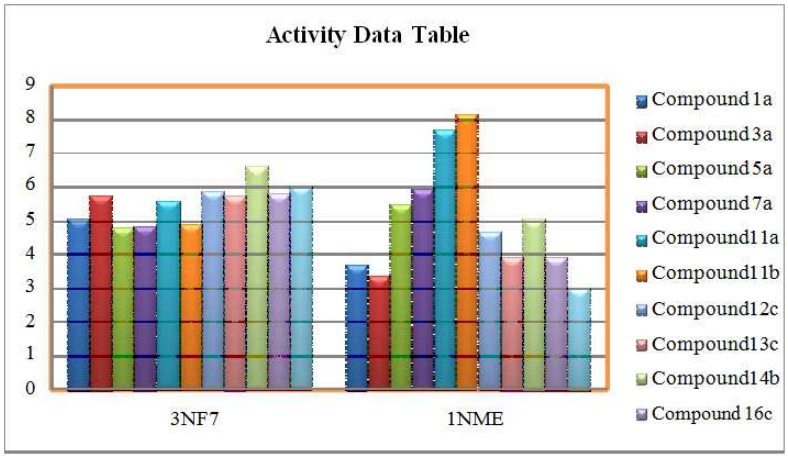


Fig. c: Activity data table

CONCLUSION

The results obtained reveal that some Isatin sulfonamide compounds exhibit anti HIV activity. QSAR and Pharmacophore Modelling study were carried out to find the best activity. The selected compounds were studied by Docking using GLIDE software. Integrase (3NF7) and caspase (1NME) were taken for study; finally ten compounds possess good activity for both the two proteins.

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