Virtual Screening of Raltegravir which was First Hiv-1 Integrase Inhibitor

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ABSTRACT:

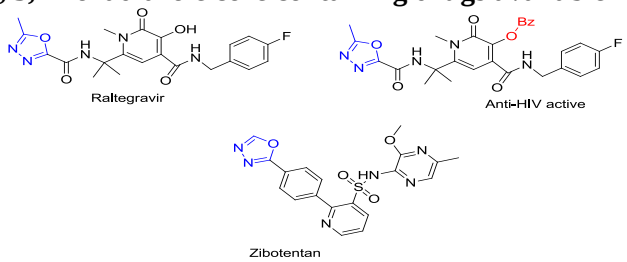
In order to understand the importance of designed, synthesized target molecules containing 1,3,4-oxadiazole moiety, we have taken one of the renowned market available drug in each category as Raltegravir as a case study. Raltegravir was FDA approved the first HIV-1 integrase inhibitor which is used in the treatment of HIV-1 infection Literature survey reveals the various biological importance and docking properties of this moiety so in this research article especially highlight on the pharmaco features of standard chosen drug and synthesized analogues which contain core molecule 1,3,4-oxadiazole based on the active site of protein and also the properties of the ligands. The 3D pharmacophore modeling is a widely utilized method in the computer-aided drug design process. It was used to identify the critical chemical features of synthesized 1,3,4-oxadiazole derivatives with S-adenosyl homocysteine nucleosidase (PDB ID: 4YML) for anti-bacterial activity and docking interactions with Pencillin Binding Protein (PDB ID: 1VQQ) for anti-fungal activity.

KEYWORDS: Raltegravir, pharmaco features, 1,3,4-oxadiazole, computer-aided drug design.

INTRODUCTION:

Virtual screening of databases can be used to validate the quality of selected pharmacophore model which was generated based on the known inhibitory activity value of compounds as well as to pick the novel and potent molecule which satisfy all critical chemical features of the hypothesis for further drug development. The initial stage of the hypothesis generation is constructive phase which considers all possible pharmacophore configurations of the most active compounds to entail pharmacophore demands[1]. The following chemical features were selected using Feature mapping, to get the essential information for hypothesis generation process: HBA, HBD, RA, Hy-Ali, positive ionization (PI), negative ionization (NI), and hydrophobic aromatic (Hy-Ar).

Figure 1: Structures of 1, 3, 4- oxadiazole core containing drugs available in the market



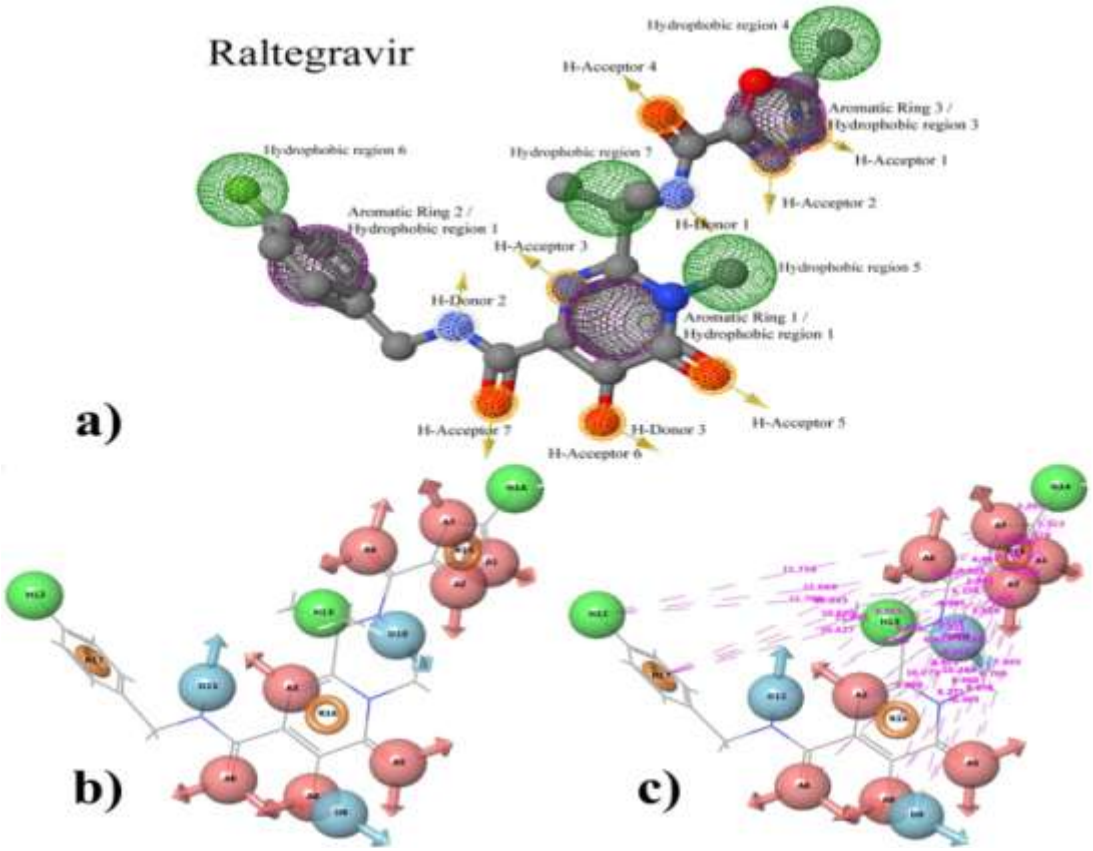
1, 3, 4-oxadiazole core containing synthesized biologically evaluated molecule used in clinical medicine as Raltegravir® an antiretroviral drug[2,3] and Zibotentan® an anticancer agent[4] Tiodazosin® and Nesapidil® as hypertensive agent, anti-HIV agent derived from raltegravir by the 5-hydroxyl group of the pyrimidine ring.[5-8] Furamizole® as antibiotics.[9]They are also useful as HIV integrase inhibitors and the angiogenesis inhibitors[10]

A 3D pharmacophore modelling method is also useful to understand 1,3,4 -Oxadiazole core containing Raltegravir compound. ZINCPharmer online server based pharmacophore features mapping was carried out to visualize the location of each pharmacophore feature of particular compound. For estimating the exact positioning, direction and distance between the identified pharmacophore features; we have used Schrodinger's pharmacophore modeling module.

The drug-like property calculation was performed by applying Lipinski's rule of five[11] and ADMET. Lipinski's rule of five is a simple model to forecast the absorption and intestinal permeability of a compound. According to the rule of five, compounds are considered likely to be well absorbed when they possess Log*P* less than 5, molecular weight less than 500, number of hydrogen bond donors less than 5, number of hydrogen bond acceptors less than 10 and number of rotatable bonds less than 10.

Figure 2: Pharmacophore features of Raltegravir compound:

a) ZINCPharmer online server based pharmacophore features mapping showing location and direction of three aromatics rings; seven hydrophobic regions; three hydrogen donors and seven hydrogen acceptors.
b) Schrodinger software based pharmacophore features mapping.
c) Distance involved between 1,3,4-Oxadiazole ring and other pharmacophore features of the compound.



MATERIAL AND METHODS:

Manual Pharmacophore hypothesis generation module of Schrodinger's maestro v9.6 was used for Pharmacophore features mapping of the compounds along with location and calculation of distance between the pharmacophore features.

Table 1: XYZ co-ordinates and radius of each pharmacophore feature of Raltegravir compound:

S.No	Pharmacophore feature	X	Y	Z	Radius
1.	Aromatic ring 1	0.11	-7.99	-0.06	1.10
2.	Aromatic ring 2	-5.99	-9.56	3.23	1.10
3.	Aromatic ring 3	0.02	-1.13	-0.01	1.10
4.	Hydrogen Donor 1	0.07	-4.50	0.83	0.50
5.	Hydrogen Donor 2	-3.05	-9.58	1.07	0.50
6.	Hydrogen Donor 3	0.05	-10.22	-1.67	0.50
7.	Hydrogen acceptor 1	0.01	-0.77	-1.06	0.50
8.	Hydrogen acceptor 2	0.03	-2.00	-0.69	0.50
9.	Hydrogen acceptor 3	-0.88	-7.78	0.82	0.50
10.	Hydrogen acceptor 4	0.06	-3.22	2.65	0.50
11.	Hydrogen acceptor 5	2.09	-8.30	-1.74	0.50
12.	Hydrogen acceptor 6	0.05	-10.22	-1.67	0.50
13.	Hydrogen acceptor 7	-2.12	-10.81	-0.53	0.50
14.	Hydrophobic region 1	0.11	-7.99	-0.06	1.00
15.	Hydrophobic region 2	-5.99	-9.56	3.23	1.00
16.	Hydrophobic region 3	0.02	-1.13	-0.01	1.00
17.	Hydrophobic region 4	-0.02	1.50	0.01	1.00
18.	Hydrophobic region 5	2.20	-6.08	-0.18	1.00
19.	Hydrophobic region 6	-7.71	-8.66	5.16	1.00
20.	Hydrophobic region 7	0.09	-5.74	2.23	1.00

Table 2: Distances between each pharmacophore features with other within the Raltegravir compound:

S.No	Site 1	Site 2	Distance in angstroms	Site 1	Site 2	Distance in angstroms
1.	A1	A2	1.287	A5	R16	2.615
2.	A1	A3	7.311	A5	R17	9.567
3.	A1	A4	4.441	A6	A7	10.365
4.	A1	A5	7.845	A6	A8	2.52
5.	A1	A6	10.279	A6	D9	3.442
6.	A1	A7	2.138	A6	D10	6.631
7.	A1	A8	9.468	A6	D11	3.088
8.	A1	D9	9.624	A6	H12	8.257
9.	A1	D10	3.905	A6	H13	6.346
10.	A1	D11	8.981	A6	H14	12.505
11.	A1	H12	12.669	A6	R15	9.93

12.	A1	H13	6.136	A6	R16	3.628
13.	A1	H14	2.512	A6	R17	5.537
14.	A1	R15	1.107	A7	A8	9.811
15.	A1	R16	7.288	A7	D9	10.089
16.	A1	R17	11.475	A7	D10	3.955
17.	A2	A3	6.039	A7	D11	8.565
18.	A2	A4	3.555	A7	H12	11.759
19.	A2	A5	6.709	A7	H13	5.157
20.	A2	A6	9.068	A7	H14	2.539
21.	A2	A7	2.144	A7	R15	1.139
22.	A2	A8	8.271	A7	R16	7.279
23.	A2	D9	8.465	A7	R17	10.843
24.	A2	D10	2.62	A8	D9	0.967
25.	A2	D11	7.789	A8	D10	5.859
26.	A2	H12	11.766	A8	D11	4.719
27.	A2	H13	4.941	A8	H12	10.448
28.	A2	H14	3.578	A8	H13	6.133
29.	A2	R15	1.111	A8	H14	11.841
30.	A2	R16	6.019	A8	R15	9.239
31.	A2	R17	10.427	A8	R16	2.751
32.	A3	A4	5.001	A8	R17	7.802
33.	A3	A5	3.952	D9	D10	6.151
34.	A3	A6	3.543	D9	D11	5.655
35.	A3	A7	7.043	D9	H12	11.411
36.	A3	A8	3.605	D9	H13	6.633
37.	A3	D9	4.318	D9	H14	12.035
38.	A3	D10	3.485	D9	R15	9.463
39.	A3	D11	2.495	D9	R16	3.262
40.	A3	H12	8.139	D9	R17	8.769
41.	A3	H13	2.857	D10	D11	5.516
42.	A3	H14	9.358	D10	H12	10.258
43.	A3	R15	6.762	D10	H13	2.915
44.	A3	R16	1.338	D10	H14	6.069
45.	A3	R17	5.925	D10	R15	3.437
46.	A4	A5	7.014	D10	R16	3.426
47.	A4	A6	8.513	D10	R17	8.541
48.	A4	A7	2.883	D11	H12	5.876
49.	A4	A8	8.223	D11	H13	4.498
50.	A4	D9	8.64	D11	H14	10.841

51.	A4	D10	3.089	D11	R15	8.4
52.	A4	D11	6.441	D11	R16	3.637
53.	A4	H12	9.811	D11	R17	3.468
54.	A4	H13	2.534	H12	H13	8.809
55.	A4	H14	5.409	H12	H14	13.748
56.	A4	R15	3.381	H12	R15	11.967
57.	A4	R16	5.484	H12	R16	9.422
58.	A4	R17	8.783	H12	R17	2.734
59.	A5	A6	5.048	H13	H14	7.677
60.	A5	A7	8.276	H13	R15	5.272
61.	A5	A8	2.801	H13	R16	3.423
62.	A5	D9	2.423	H13	R17	7.285
63.	A5	D10	4.545	H14	R15	2.633
64.	A5	D11	6.131	H14	R16	9.493
65.	A5	H12	11.986	H14	R17	12.98
66.	A5	H13	5.327	R15	R16	6.861
67.	A5	H14	10.181	R15	R17	10.85
68.	A5	R15	7.664	R16	R17	7.105

RESULTS AND DISCUSSION:

A result depicted in Table 1 has explained the co-ordinates and radius of each pharmacophore feature of Raltegravir compound. The Table 2 has explained all details measurements of each pharmacophore and core molecule 1,3,4-oxadiazole within the Raltegravir compound(FDA approved drug).

The donating and accepting ability of the small molecules was measured which can predict how well the group can donate or accept the electrons on the basis of Density Functional Theory (DFT).

CONCLUSION:

A good pharmacophore model should predict the correct activity range of the independent molecules which can be synthesized and evaluated *in silico*. i.e. the possible binding modes and enzyme inhibition mechanism.

In order to further understand the effect of 5-substituted-1,3,4-oxadiazole-2amine activity, we synthesized various derivatives of it and evaluated *in vitro, in silico* accordingly.

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