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# AN *IN SILICO* APPROACH TO IDENTIFY NEW ANTI-HIV INTEGRASE INHIBITOR LIKE LEADS BY DOCKING STUDIES

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**Keywords:**

HIV, Integrase inhibitors(INIs), Dolutegravir, docking, Tanimoto, Schrodinger Suite.

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**ABSTRACT:** The Human immunodeficiency virus(HIV)type-1 integrase is one of the most important target of highly active anti retrovirus therapy (HAART), due toits role to incorporate genetic information into the host DNA, so its prevention to its proper function results in very fine therapeutic effect for the treatment of all acquired immune deficiency syndrome(AIDS), extensive research work on integrase inhibitors(INIs) haven't carried out till present due to complexities in research with integrase and a very few drug are known to inhibit integrase. Dolutegravir is a new 2nd generation Integrase inhibitor (INIs) in a short list of INIs, recently approved by FDA in the list of HAART, so herein we taken Dolutegravir as a reference structure for virtually identification of more/similar efficient drug like leads then Dolutegravir using three different PDB structures (4S3O, 3S3M & 3S3N) of Integrase having in different mutated state from PDB database 'RCSB' versus chemical compounds database 'ZINC' using Schrodinger and Discovery Studio software. Using molecular constraint search with similarity coefficient 'Tanimoto', 1,65,000 ligands were extracted out and further docking analysis resulted in some better efficient in docking properties and computed medicinal parameters have been reported, and, they may further undergo through high end extensive virtual investigation and beyond, in such research laboratory where adequate research facilities are available.

**INTRODUCTION:** In silico Molecular drug design strategically very important tool in drug evaluation and optimization to more potent drug like leads, in preliminary investigation these tool make by day, very popular among medicinal chemist, these tools help to reduce cost and time frame for evaluating new drug candidate[1], traditional drug design strategy have some very known limitation, which can resolve out by using in silico techniques.

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Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV), current statistics of infected people worldwide with HIV/AIDS is 35.3 million (2012) and this statistics in 2009 at about 40 million[2, 3]. Acquired immunodeficiency syndrome (AIDS) is presently one of the leading disease which causes death in the world.

Global statistic reveals that new infection rate gradually going down by day, but still this disease worldwide categorically very dangerous, the recovery and rehabilitation from this disease is not easy and straightforward and medication only improve somewhat infection conditions under control. The life- cycle of human immune

deficiency virus type-1(HIV-1) involves the intervention of multiple enzymes, most of them have been studied as potential drug target for the pharmacological response to prevent the disease HIV/AIDS. Among the list of these enzymes, one of them, HIV-1 integrase (IN) has a crucial role to catalyzes the integration between viral DNA to host DNA Strand, this process important for virus replication cycle [4], because human itself no such type of enzymes, so inhibition mechanism is selective without interference, Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle [5], on the basis of this mechanism of action we induce this work to find out more potent new INIs as similar to Doleutegravir, effective against mutant and wild both type of integrase, with better binding and medicinal properties simultaneously, fully on the basis of "in silico" techniques.

**Dolutegravir:**

Dolutegravir (GSK1349572) is an anti-retroviral drug under the umbrella of integrase inhibitors ($2^{nd}$ generation) approved in 13 August 2013 by FDA marketed as brand name 'Tivicay' by GlaxoSmithKline (GSK) for use in a broad population of HIV-infected patients, which is used for hindering the activity of the integrase to its proper functionality in HIV [6].

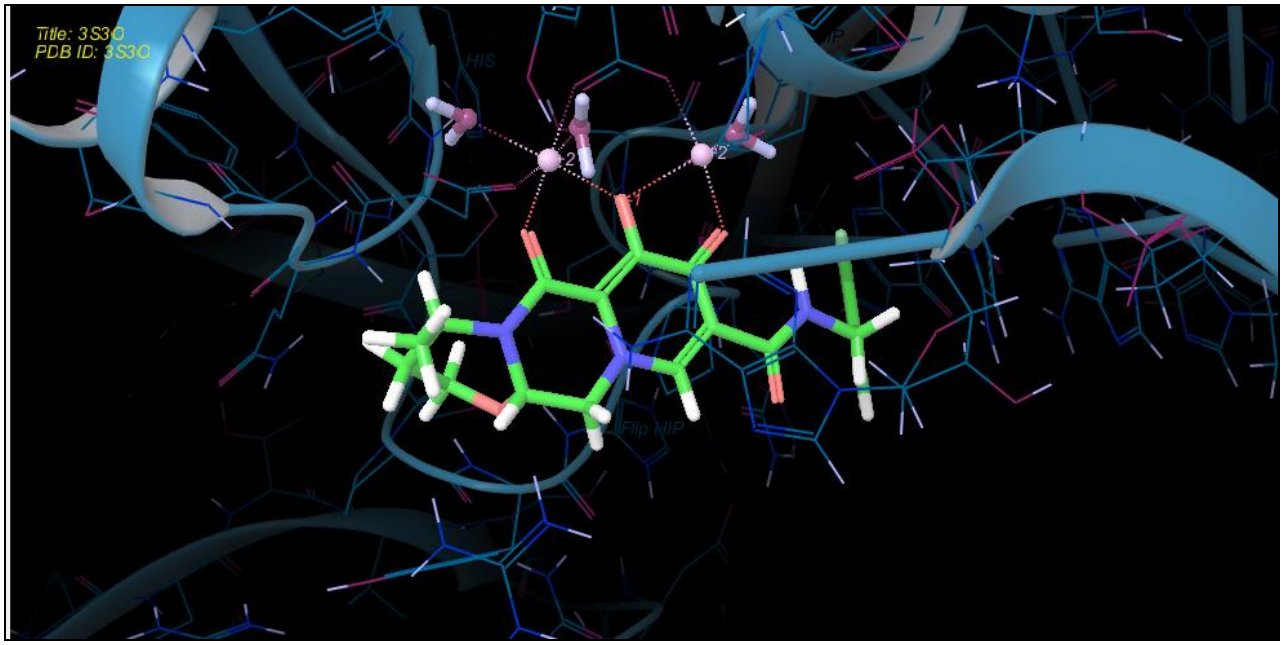
In the work herein Dolutegravir is taken as reference molecule and find out 1% of similar molecules of each retrieved files of zinc drug bank (sd file) using similarity coefficient "Tanimoto" in DS 2.5.In a single job around 1350 molecules was found out molecular structures as similar to Dolutegravir, we performed as like total 118 jobs and a total 118×1350 molecules we found out and perform docking in Schrodinger software.

**TABLE 1: DIFFERENT Pdb(INTEGRASE), LIGAND, CRYSTALLOGRAPHIC PROPERTIES AND MUTATION DETAILS**

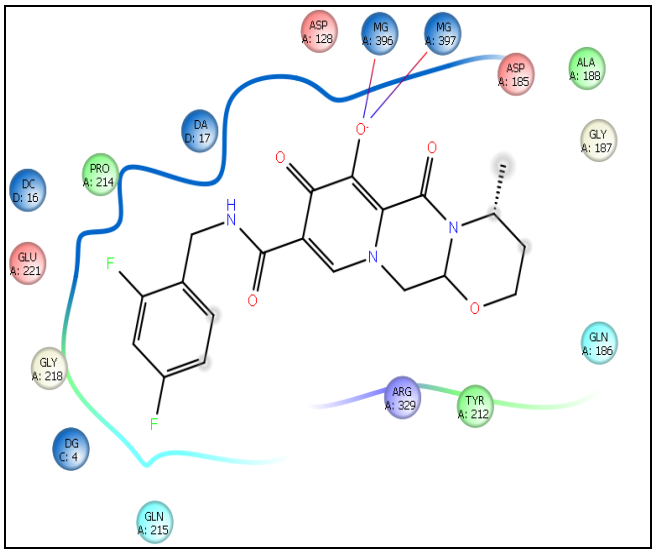
| Pdb | Ligand | Resol. | R Value | R Free | Mutation(S) |
|---|---|---|---|---|---|
| 3S3O | Dolutegravir | 2.55 | 0.209(Obs.) | 0.230 | G968S, N975H |
| 3S3M | Dolutegravir | 2.49 | 0.207(Obs.) | 0.232 | Wild |
| 3S3N | Dolutegravir | 2.49 | 0.211(Obs.) | 0.232 | G968S |

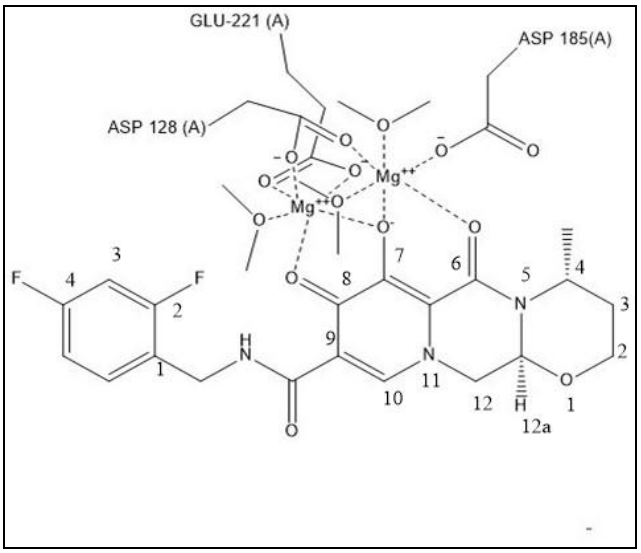
**Integrase:** The HIV-1 integrase is one of the most important targets of antiretroviral therapy used in the treatment of AIDS, this HIV protein has an important key role in viral replication as a catalytic protein that inserts the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication blocking it can halt further spread of the virus.[7]

Today a sufficient number of X-RAY crystallographic structures of HIV-1 integrase co-complexed with Dolutegravir are available on the rcsb.org, so for our research concerns we retrieved following 3S3O, 3S3M &3S3N(see **Table 1**) Pdb files as target having complexed with inhibitor Dolutegravir((4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo- 3, 4, 6, 8, 12, 12a-hexahydro- 2H - pyrido[1',2':4,5] pyrazino [2,1-b][1,3]oxazine-9 carboxamide), An integrase strand transfer inhibitors INSTI). Crystal structure analysis of HIV-1 Integrase shows that Dolutegravir is surrounded with following amino acids GLY-187(A), ALA-188(A), ASP-185(A), ASP-128(A), PRO-214(A), GLY-218(A), GLU-221(A), ARG-329(A), TYR-212(A) & GLN-186(A) with totally on non-bonded interactions, in Dolutegravir at position "7"hydroxyl group is in ionised state and ASP185(A), ASP 128(A), GLU 221(A) of Integrase and three water molecules create two individual hexadendate coordination spheres around the two $Mg^{2+}$ ions at the Dolutegravir binding site (see **Fig.1.1**) in the $Mg^{2+}$ 396(A) coordination sphere"6" Oxo, "7" phenoxide group of Dolutegravir, two water molecules, Asp 185(A)& Asp 128(A) as a bridging manner complete the coordination sphere around it and in the coordination sphere charge is balanced another $Mg^{2+}$ center 397(A) coordinated to "7" phenoxide , "8" Oxo of Dolutegravir, Glu-221(A)(bidendate manner to same coordination sphere), Asp-221(A) as a bridging bidendate manner and a water molecule complete the hexadendate coordination sphere around it, So by this interaction the doleutegravir halted the integrase to incorporation of viral DNA to the host(Human) DNA.




**(A)**




**(B)** **(C)**

**FIG.1: (A) DOLUTEGRAVIR DOCKED IN PDB 3S3O, (B) ITS INTERACTION DIAGRAM SURROUNDED AMINO ACIDS IN INTEGRASE AND (C) IN THE $Mg^{2+}$ COORDINATION SPHERE**

**Experiment:** X-ray crystallographic structuredata of HIV-1 integrase co-crystallized with INIs Dolutegravir retrieved as pdb file 3S3O, 3S3M & 3S3N from rcsb.org and prepared in protein preparation wizard of maestro with the following steps- preprocess(default settings), deleting all unnecessary water molecules and other structures except Dolutegravir and coordinated two $Mg^{2+}$ ionswith it, added hydrogen, generated it states, optimization, and minimization (with OPLS2005 force field)with default constraint of the 0.3Å of RMSD and corresponding Grid are generated in these prepared pdbs with the Centre defined by the co-crystalized ligand Dolutegravir with defaultsettings included partial charge and saved all in pre-created directory folder.

Ligands extracted as previously mentioned procedure as similar to Dolutegravirwith DS V2.5 in job " find similar molecules" with settings 1% similar molecules to "Dolutegravir" with similarity coefficient "tanimoto" which is very well known accurate similarity measures, 118 such jobs were done and atotal 1,65,000 molecules are extracted out, which are structurally similar to Dalutegravir. These structurally similar moleules are prepared for

docking jobs in 'ligprep' with force-field OPLS 2005 using "epik" with deselected options 'desalt' and selected 'generate tautomer' afterwards docking analysis were done in glide programme of maestro, better then dolutegravir in docking score were separated out, whose docking score more than Dolutegravir selectively prepared in 'ligprep' with force field OPLS 2005 using 'epik' and with better protocol setting, docking again done in corresponding grid of pdb in glide programme. All docking calculations were performed using the "Extra Precision"(XP) mode of Glide Program with settings including sampling ligands 'flexible', optionally available various protocols for ligands constraints as rewards measure, partial charge of ligands and similarity measures to Dolutegravir were included.

All jobs were done on Intel i-7 3770K (unlocked) quad core machine with bios setting 3.9-4.4GHz with G Skill 16 GB RAM & Corsair H70 liquid cooling system. Medicinal parameter were calculated using programme qik prop (**Table 2-6)**

**RESULT AND DISCUSSION:**

In our virtual study we found out following molecules (for full detail see in **Table**: 3S3M, 3S3N &3S3O**)** ZINC05773622, ZINC09419358, ZINC13235074, ZINC00902842,ZINC71766163,ZINC30587747,ZINC05773618 ZINC16851339, ZINC09716706, ZINC76826280,ZINC04602981, ZINC64567237, ZINC00847009, ZINC64567242 ZINC04602980, ZINC05773618,ZINC83259749,ZINC16851339, ZINC64567237, ZINC00902842, ZINC01413197 ZINC49477784,ZINC06748332,ZINC09716706,ZINC13316188, ZINC76826280, ZINC06880639, ZINC06880637 ZINC65435841 & ZINC76826243 showing better binding capacity in "3S3O" PDB (Integrase)which is in highest mutated state(G968S, N975H) in three PDBs(see **Table 1**) which we have taken in interest for this work, in table- 3S3O the Doleutegravir is in bottom left in docking score so least effectively bind to proper active site to its pharmalogical response to halt the integrase role play in the biochemistry of HIV-1 life cycle, binding pose and its interaction diagram of some invesigated molecules are listed in **Fig.1.2** and binding pattern is almost the same as Dolutgravir in which the interaction with two $Mg^{2+}$ ion is necessarily maintain in each individuals and co ordination sphere is frequently as same maintain and some new non-bonded interaction inhanced the binding efficacy in the proper active site.

In medium mutated state integrase PBD "3S3N", the trend to binding is maintained with somewhat less efficacy and following molecules ZINC05773622, ZINC04602980, ZINC00902842, ZINC12997463, ZINC05773618, ZINC76826280, ZINC04705122, ZINC76825896, ZINC04377488, ZINC13235071, ZINC23138667, ZINC76826243, ZINC65435838, ZINC04602981, ZINC13235074, ZINC09419358, ZINC71284549, ZINC13235071, ZINC76826270, ZINC08846498, ZINC71284548, ZINC02211439, ZINC02402950, ZINC12997461, ZINC83259758, ZINC00078125, ZINC06741729, ZINC83293938, ZINC23138667, ZINC01739118, ZINC35898180, ZINC39349711 & ZINC06726134 were got crowned for better then Dolutegravir in docking scores but most of them were least favorable then dolutegravir in wild PDB "3S3M"(see **Table-**3S3M) so out come of these result showing that these molecules are more effective in mutated state of integrase on binding context, all reporting molecules herein are showing CNS activity in between -1 to -2 (-2 is necessarily better) lipophilic computed data is almost as same as Dolutegravir, reactive functional group(rtvFG) in dolutegravir is none and all reported molecules are in between 0 to 1 so almost as dolutegravir, QPlogBB (Predicted brain/blood partition coefficient) and other computed properties as similar to dolutegravir, and all are in required limit.

**TABLE: 3S3M**

| Title | D.S. | Lip | rtvFG | CNS | dipole | donorHB | accptHB | QPPCaco | QPlogBB | QPPMDCK | metab | QPlogKhsa | PHOAbs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ZINC13235071 | -12.1 | -5.69 | 0 | -2 | 8.647 | 3.25 | 3.25 | 58.344 | -1.164 | 153.732 | 3 | 0.112 | 82.917 |
| Dolutegravir | -12.1 | -4.7 | 0 | -2 | 6.201 | 0 | 8.45 | 343.417 | -1.009 | 416.461 | 3 | -0.387 | 85.753 |
| ZINC09419358 | -11.9 | -4.46 | 0 | -2 | 3.703 | 3 | 8.25 | 27.613 | -1.118 | 37.534 | 3 | -1.117 | 65.186 |
| ZINC09419358 | -11.9 | -4.48 | 0 | -2 | 4.544 | 3 | 8.25 | 26.522 | -1.126 | 36.747 | 3 | -1.118 | 64.808 |
| ZINC05773622 | -11.9 | -5.06 | 0 | -1 | 8.671 | 2 | 4.5 | 158.484 | -0.758 | 306.458 | 4 | -0.244 | 87.113 |
| ZINC23138667 | -11.7 | -6.37 | 0 | -1 | 4.875 | 2 | 6 | 836.603 | -0.717 | 1526.892 | 5 | 0.288 | 100 |

(D.S. (Docking Score, kcal/mol), Lip (Lipophilicity), rtvFG (no. of reactive functional groups, 0 – 2), CNS (Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale), Dipole(computed dipole moment, 1.0 – 12.5), donarHB (Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. Values are averages taken over a number of configurations, so

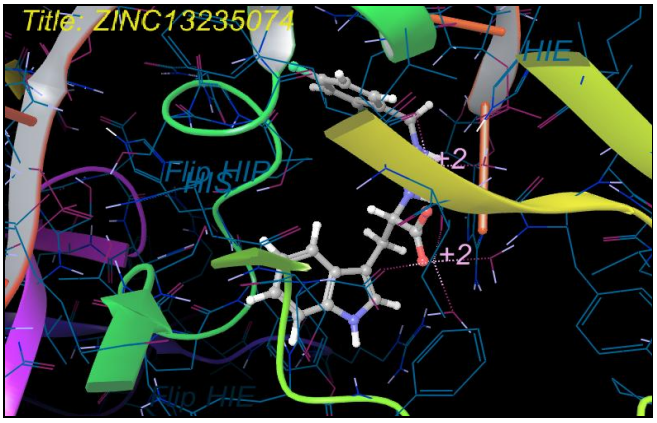
they can be non-integerm, 0.0 – 6.0), accptHB (Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer, 2.0 – 20.0), QPPCaco(Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut blood barrier. QikProp predictions are for non-active transport, <25 poor, >500 great), QPlogBB(Predicted brain/blood partition coefficient, –3.0 – 1.2), metab (Number of likely metabolic reactions, 1-8), QPlogKhsa(Prediction of binding to human serum albumin, –1.5 – 1.5 ), PHOAbs(Predicted human oral absorption on 0 to 100% scale, >80% is high, <25%ispoor)

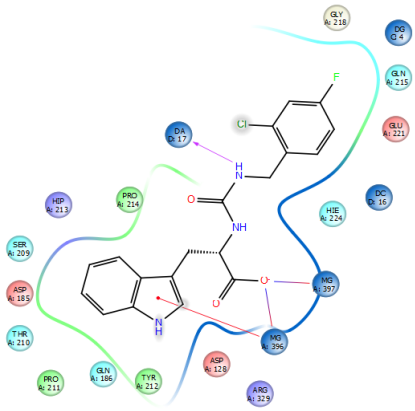
**TABLE: 3S3N**

| Title | D.S. | Lip | rtvFG | CNS | dipole | donorHB | accptHB | QPPCaco | QPlogBB | QPPMDCK | metab | QPlogKhsa | PHOAbS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ZINC05773622 | -12.48 | -5.3 | 0 | -1 | 9.343 | 2 | 4.5 | 111.029 | -0.899 | 236.239 | 4 | -0.198 | 84.724 |
| ZINC04602980 | -12.43 | -5.42 | 0 | -1 | 6.162 | 2 | 4.5 | 161.769 | -0.758 | 306.931 | 4 | -0.207 | 87.857 |
| ZINC00902842 | -12.27 | -4.1 | 0 | -1 | 5.578 | 0 | 6.25 | 632.888 | -0.878 | 545.729 | 5 | 0.101 | 100 |
| ZINC12997463 | -12.19 | -3.33 | 0 | -1 | 6.085 | 3 | 6.5 | 9.339 | -0.473 | 14.823 | 3 | -0.715 | 47.506 |
| ZINC05773618 | -12.16 | -5.14 | 0 | -1 | 7.043 | 2 | 4.5 | 143.064 | -0.848 | 280.53 | 4 | -0.164 | 87.545 |
| ZINC76826280 | -11.77 | -5.64 | 1 | -2 | 3.369 | 1 | 3.75 | 717.909 | -1.175 | 477.092 | 3 | 0.7 | 100 |
| ZINC04705122 | -11.53 | -4.54 | 0 | -1 | 3.373 | 2 | 5.7 | 311.308 | -0.345 | 885.943 | 4 | 0.181 | 96.964 |
| ZINC76825896 | -11.52 | -5.55 | 1 | -2 | 5.476 | 1 | 5.75 | 487.176 | -1.3 | 410.417 | 3 | 0.316 | 100 |
| ZINC04377488 | -11.42 | -3.27 | 0 | -1 | 7.55 | 2 | 4.5 | 174.538 | -0.799 | 459.708 | 3 | 0.572 | 85.477 |
| ZINC13235071 | -11.41 | -5.78 | 0 | -2 | 4.136 | 3.25 | 3.25 | 50.873 | -1.113 | 178.51 | 3 | 0.132 | 82.422 |
| ZINC23138667 | -11.41 | -6.08 | 0 | -1 | 6.1 | 2 | 6 | 867.944 | -0.721 | 1519.594 | 5 | 0.272 | 100 |
| ZINC76826243 | -11.4 | -5.48 | 1 | -2 | 7.15 | 1 | 5.75 | 482.949 | -1.337 | 353.555 | 3 | 0.331 | 100 |
| ZINC65435838 | -11.32 | -4.35 | 0 | -2 | 3.847 | 1.25 | 7.75 | 19.168 | -1.779 | 23.651 | 5 | -0.712 | 59.634 |
| ZINC04602981 | -11.27 | -4.32 | 0 | -1 | 6.134 | 2 | 4.5 | 177.266 | -0.668 | 342.366 | 4 | -0.249 | 88.062 |
| ZINC13235074 | -12.21 | -5.48 | 0 | -2 | 6.971 | 3.25 | 3.25 | 48.671 | -1.347 | 137.566 | 3 | 0.174 | 82.34 |
| ZINC09419358 | -12.12 | -3.1 | 0 | -2 | 8.429 | 3 | 8.25 | 6.679 | -1.442 | 16.375 | 3 | -1.112 | 52.479 |
| ZINC71284549 | -12.03 | -4.79 | 0 | -2 | 10.172 | 2 | 9.5 | 6.802 | -1.04 | 18.668 | 4 | -1.028 | 35.996 |
| ZINC13235071 | -11.77 | -4.98 | 0 | -2 | 8.275 | 3.25 | 3.25 | 51.273 | -1.25 | 138.031 | 4 | 0.127 | 82.045 |
| ZINC76826270 | -11.69 | -5.53 | 1 | -2 | 3.747 | 1 | 3.75 | 710.91 | -1.194 | 481.511 | 3 | 0.732 | 100 |
| ZINC08846498 | -11.66 | -3.03 | 0 | -2 | 4.451 | 1 | 6.75 | 31.849 | -1.406 | 97.867 | 3 | 0.106 | 77.096 |
| ZINC71284548 | -11.64 | -4.98 | 0 | -1 | 6.807 | 2 | 9.5 | 6.446 | -0.97 | 18.882 | 4 | -1.072 | 34.788 |
| ZINC02211439 | -11.53 | -3.82 | 0 | -2 | 5.614 | 2.25 | 3.25 | 71.59 | -1.029 | 105.095 | 2 | -0.265 | 77.143 |
| ZINC02402950 | -11.49 | -3.82 | 0 | -1 | 5.623 | 2.25 | 3.25 | 92.46 | -0.872 | 177.403 | 2 | -0.222 | 80.591 |
| ZINC12997461 | -11.47 | -2.67 | 0 | -1 | 3.836 | 3 | 6.5 | 8.457 | -0.568 | 15.265 | 3 | -0.655 | 48.059 |
| ZINC83259758 | -11.22 | -4.25 | 1 | -1 | 3.12 | 1.25 | 6.45 | 193.738 | -0.686 | 473.48 | 2 | -0.082 | 91.589 |
| ZINC00078125 | -11.17 | -3.45 | 0 | -2 | 4.892 | 0 | 6.25 | 313.765 | -1.013 | 255.748 | 5 | -0.32 | 84.433 |
| ZINC06741729 | -11.12 | -4.02 | 0 | -1 | 5.786 | 2 | 4.5 | 190.305 | -0.581 | 245.049 | 7 | -0.198 | 86.037 |
| ZINC83293938 | -11.09 | -3.72 | 1 | -1 | 7.041 | 1.25 | 5.5 | 175.154 | -0.77 | 374.345 | 2 | 0.118 | 92.487 |
| ZINC23138667 | -11.07 | -5.74 | 0 | -1 | 6.94 | 2 | 6 | 844.065 | -0.724 | 1542.638 | 5 | 0.288 | 100 |
| ZINC01739118 | -11.07 | -3.98 | 0 | -1 | 2.83 | 2 | 4.5 | 156.869 | -0.594 | 384.131 | 1 | -0.063 | 86.91 |
| ZINC35898180 | -11.07 | -4.04 | 0 | -1 | 7.595 | 2 | 4.5 | 179.261 | -0.506 | 253.278 | 5 | -0.334 | 84.764 |
| ZINC39349711 | -11.04 | -4.04 | 0 | -1 | 7.729 | 2 | 4.5 | 183.05 | -0.502 | 256.333 | 3 | -0.31 | 83.929 |
| ZINC06726134 | -11.04 | -4.04 | 0 | -1 | 7.75 | 2 | 4.5 | 182.995 | -0.492 | 255.722 | 3 | -0.317 | 83.803 |
| Dolutegravir | -11.11 | -4.57 | 0 | -1 | 7.362 | 0 | 8.45 | 406.604 | -0.916 | 504.233 | 3 | -0.408 | 87.152 |

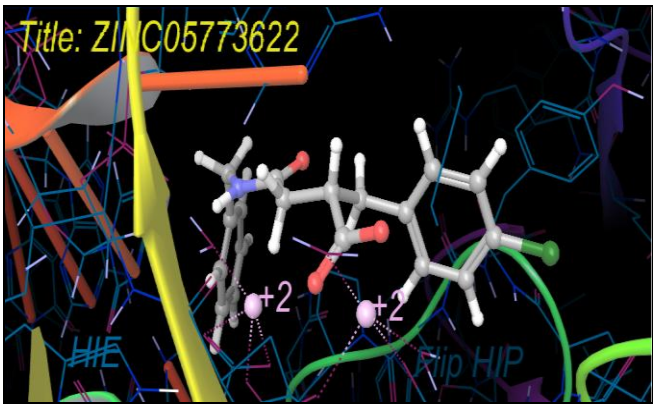
**TABLE: 3S3O**

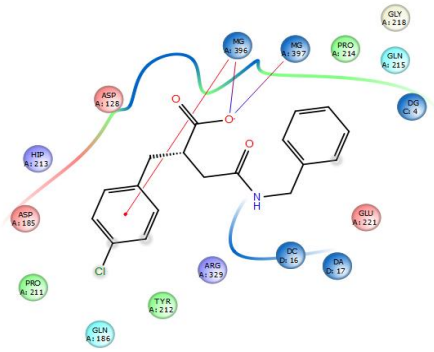
| Title | D.S. | Lip | rtvFG | CNS | donorHB | accptHB | QPlogHERG | QPPCaco | QPlogBB | QPPMDCK | metab | QPlogKhsa | PHOAbs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ZINC05773622 | -13.03 | -5.37 | 0 | -1 | 2 | 4.5 | -2.624 | 134.82 | -0.774 | 289.898 | 4 | -0.223 | 86.122 |
| ZINC09419358 | -12.23 | -4.69 | 0 | -2 | 3 | 8.25 | -0.733 | 27.06 | -1.128 | 37.119 | 3 | -1.115 | 65.007 |
| ZINC13235074 | -12.2 | -5.28 | 0 | -1 | 3.25 | 3.25 | -2.791 | 94.126 | -0.963 | 225.657 | 3 | 0.068 | 86.546 |
| ZINC00902842 | -11.98 | -4.39 | 0 | -1 | 0 | 6.25 | -5.275 | 687.692 | -0.949 | 597.29 | 5 | 0.161 | 100 |
| ZINC71766163 | -11.87 | -2.28 | 0 | -1 | 2 | 4.4 | -1.449 | 79.677 | -0.661 | 201.05 | 2 | -0.686 | 70.536 |
| ZINC30587747 | -11.85 | -5.07 | 0 | -2 | 2 | 8.25 | -5.267 | 138.602 | -1.653 | 271.177 | 3 | -0.149 | 81.309 |
| ZINC05773618 | -11.79 | -4.95 | 0 | -1 | 2 | 4.5 | -2.944 | 140.875 | -0.846 | 275.234 | 4 | -0.198 | 86.839 |
| ZINC16851339 | -11.44 | -6.23 | 0 | -2 | 2 | 6 | -5.353 | 269.006 | -1.063 | 1256.394 | 3 | 0.156 | 92.412 |
| ZINC09716706 | -11.34 | -3.39 | 0 | -1 | 0 | 6 | -4.874 | 341.875 | -0.951 | 309.943 | 6 | -0.462 | 82.912 |
| ZINC76826280 | -11.33 | -5.68 | 1 | -2 | 1 | 3.75 | -6.399 | 736.033 | -1.114 | 576.884 | 3 | 0.675 | 100 |
| ZINC04602981 | -11.31 | -4.75 | 0 | -1 | 2 | 4.5 | -2.165 | 120.807 | -0.802 | 235.452 | 4 | -0.284 | 83.789 |
| ZINC64567237 | -11.29 | -5.85 | 0 | -2 | 2 | 6 | -4.974 | 309.642 | -1.005 | 1112.01 | 4 | 0.208 | 93.602 |
| ZINC00847009 | -11.28 | -4.23 | 1 | -2 | 1 | 6.45 | -5.696 | 208.908 | -1.468 | 206.347 | 3 | 0.307 | 89.322 |
| ZINC64567242 | -11.19 | -5.63 | 0 | -1 | 2 | 4.5 | -5.137 | 353.691 | -0.983 | 1302.396 | 4 | 0.298 | 96.848 |
| ZINC04602980 | -11.88 | -4.76 | 0 | -1 | 2 | 4.5 | -2.702 | 112.447 | -0.88 | 234.578 | 4 | -0.216 | 84.422 |
| ZINC05773618 | -11.74 | -5.12 | 0 | -1 | 2 | 4.5 | -2.959 | 149.587 | -0.819 | 292.684 | 4 | -0.203 | 87.359 |
| ZINC83259749 | -11.66 | -5.73 | 1 | -1 | 1.25 | 6.45 | -4.396 | 142.999 | -0.731 | 1970.02 | 2 | 0.286 | 84.063 |
| ZINC16851339 | -11.65 | -6.51 | 0 | -2 | 2 | 6 | -5.291 | 265.469 | -1.066 | 1208.868 | 3 | 0.149 | 92.104 |
| ZINC64567237 | -11.56 | -6.18 | 0 | -2 | 2 | 6 | -4.957 | 310.553 | -1.012 | 1090.719 | 4 | 0.205 | 93.535 |
| ZINC00902842 | -11.53 | -4.2 | 0 | -1 | 0 | 6.25 | -4.699 | 702.235 | -0.822 | 610.571 | 5 | 0.136 | 100 |
| ZINC01413197 | -11.44 | -4.26 | 1 | -2 | 1 | 6.45 | -5.892 | 198.858 | -1.565 | 184.908 | 3 | 0.241 | 87.832 |
| ZINC49477784 | -11.42 | -3.17 | 0 | -1 | 2 | 6.2 | -1.142 | 99.846 | -0.756 | 210.793 | 4 | -0.719 | 74.092 |
| ZINC06748332 | -11.37 | -5.16 | 0 | -1 | 2 | 6 | -5.915 | 421.777 | -0.839 | 788.419 | 4 | 0.528 | 96.426 |
| ZINC09716706 | -11.34 | -3.39 | 0 | -1 | 0 | 6 | -4.858 | 336.7 | -0.954 | 304.871 | 6 | -0.465 | 82.734 |
| ZINC13316188 | -11.16 | -4.21 | 0 | -1 | 2 | 6 | -2.414 | 173.614 | -0.799 | 247.039 | 4 | -0.448 | 83.944 |
| ZINC76826280 | -11.13 | -5.43 | 1 | -1 | 1 | 3.75 | -6.389 | 947.184 | -0.99 | 736.804 | 3 | 0.628 | 100 |
| ZINC06880639 | -11.12 | -4.34 | 0 | -1 | 2 | 4.5 | -2.017 | 202.218 | -0.395 | 828.921 | 5 | -0.212 | 89.143 |
| ZINC06880637 | -11.09 | -3.87 | 0 | -1 | 2 | 4.5 | -1.785 | 158.076 | -0.42 | 689.361 | 5 | -0.233 | 86.537 |
| ZINC65435841 | -11.04 | -4.12 | 0 | -2 | 1.25 | 7.75 | -1.615 | 24.565 | -1.67 | 24.644 | 5 | -0.761 | 60.776 |
| ZINC76826243 | -11.02 | -5.76 | 1 | -2 | 1 | 5.75 | -6.427 | 288.952 | -1.571 | 191.162 | 3 | 0.297 | 92.444 |
| Dolutegravir | -11.46 | -5.12 | 0 | -1 | 0 | 8.45 | -5.192 | 396.312 | -0.945 | 482.592 | 3 | -0.354 | 87.581 |



**(a)**



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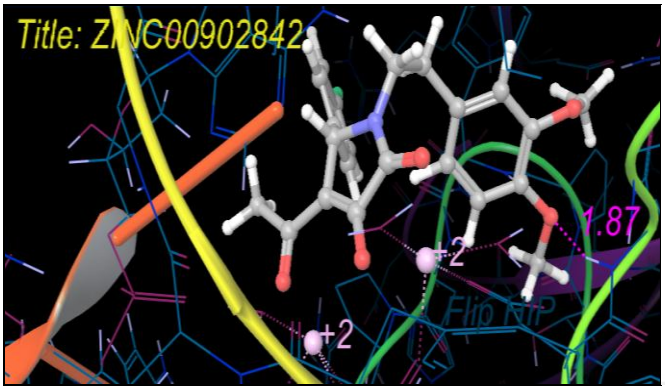
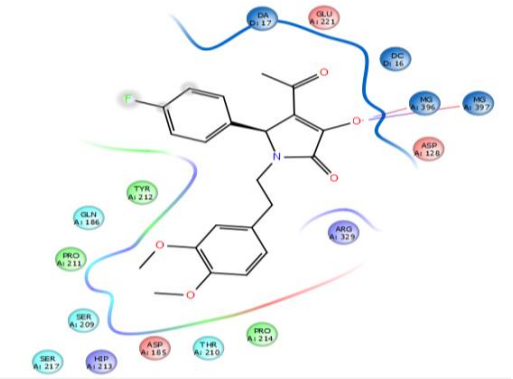
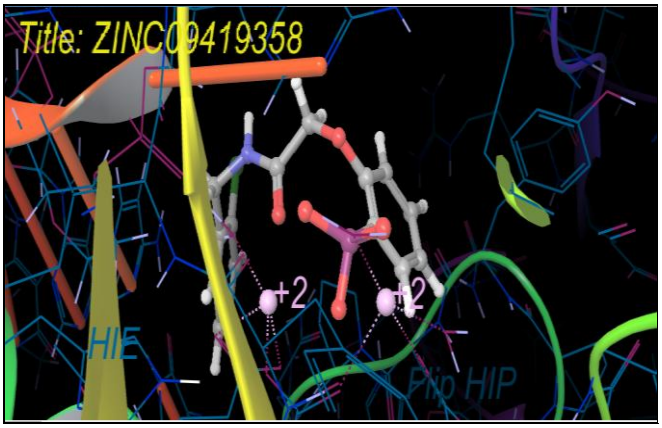
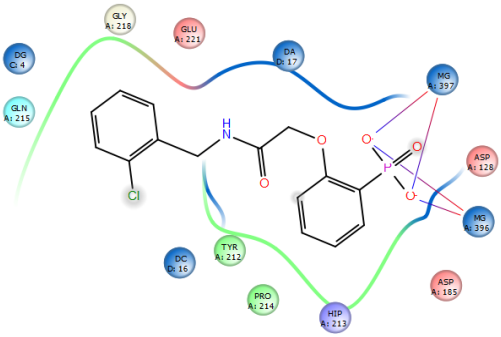


**(c)**



**(d)**

**FIG: 1.2 3S3O (INTEGRASE) DOCKED LIGAND POSE AND ITS CORRESPONDING INTERACTION DIAGRAM FOR (a) ZINC1323507 (b )ZINC05773622, (c) ZINC00902842 & (d) ZINC09419358**

**CONCLUSION:** In this work, we have tried to recognized some more/similar potent drug like leads namely coded ZINC13235071(((2-chloro-4-fluorobenzyl)carbamoyl)-D-tryptophanate), ZINC 05773622((S)-4-(benzylamino)-2-(4-chlorobenzyl)-4-oxobutanoate), ZINC00902842 ((S)-4-acetyl-1-(3,4-dimethoxyphenethyl)-5-(4-fluorophenyl) – 2 -oxo-2,5-dihydro-1H-pyrrol-3-olate), ZINC 1323 5074(((2-chloro-4-fluorobenzyl)carbamoyl) – L -tryptophanate) & ZINC09419358(((2-chloro-4-fluorobenzyl) carbamoyl)-D-tryptophanate) instead 'Dolutegravir' these may be more effective, we used three different Integrase crystallographic structures for better identification/verification of our results and showing very fine computed properties, this study verify the importance of small drug like molecular libraries as like 'ZINC.docking.org'and their use certainly help scientific groups to enhance their capabilities in drug discovery with reducing time, including drug discovery process prior synthesis. Herein identified molecules may further investigate instead "in silico", where experimental facility are adequately available.

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