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Prediction of physic-chemical property/ Biological Activity and ADMET (absorption, distribution, mechanism, excretion, and toxicity) parameters of approved HIV Medications

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Abstract— The purpose of this short study is to estimate the main chemical-physical properties, pharmacokinetics, and biological activity of the main anti-HIV drugs. The ADMETlab, pkCSM server, and The Pass Online Server were used to complete this computational investigation. The canonical SMILES strings of these compounds were retrieved from PubChem (http://pubchem.ncbi.nlm.nih.gov/) using their CAS registry number or chemical name(s). Regarding the in Silico toxicity study, between all the HIV antivirals investigated, "Lamivudine/Zidovudine", sold under the brand name "Combivir", reported good overall values, indicating that it is potentially the least toxic, except for the Minnow toxicity parameter (LC50 with a value of about 7.025 (log mM). Furthermore, Lopinavir also reported overall acceptable values against the various toxicity tests, except that of the Max. tolerated dose (human) with a value of -0.297 (log mg / kg / day in units), compared to Combivir of 0.684 log mg / kg / day in units. From this evaluation, Combivir is one of the best drugs, manly in terms of toxicity parameters and also it would be useful to focus on discovering similar chemical structures, based on their structure.

Keywords— *HIV, Drug –likeness analysis, toxicity estimation and ADME/T evaluation.*

I. INTRODUCTION

Nowadays, Pharmacology plays a primary role, in studying drugs and the interactions that take place between them and living organisms. Several online servers are available, making possible the prediction of the different chemical-physical and pharmacological characteristics of drugs with excellent reliability, to lower production costs, and focus in a targeted way in therapy research. It is important to know the mechanism of action, toxicity, dosage, effectiveness, selectivity, and potency of drugs. This short communication aims to predict accurately Physicochemical Property, for instance, LogS (Solubility), LogD (Distribution Coefficient D at PH=7.4), and LogP (Distribution Coefficient P) of main approved HIV drugs. HIV is a member of the genus Lentivirus, part of the family Retroviridae. In the Literature are studied several cases of tuberculosis (TB) have occurred in people who are HIV positive [6,7].

It is known that the HIV virus is transmitted at any stage of the disease through unprotected sex, contact with blood, vertical transmission between mother and baby during pregnancy, childbirth, and breastfeeding [8-10]. The structure of the RNA genome of HIV-1 included nine genes (gag, pol, and env, tat, rev, nef, vif, vpr, vpu). Three of these genes, gag, pol, and env, contain the information needed to create the structural proteins for the new virus particles [11,12] . Until now, there are several FDA-Approved HIV Medicines. For more information check it out on https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines and https://www.cdc.gov/hiv/basics/livingwithhiv/treatment.html as well. In general, we can divide these drugs into different categories, depending on their target function:

1. **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**: [Abacavir (Abacavir sulfate, ABC, trade name Ziagen), Emtricitabine, trade name Emtriva), lamivudine, trade name Epivir), Tenofovir disoproxil Fumarate, brand name Viread), zidovudine, namely Retrovir)]
2. **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** : [Doravirine, called Pifeltro), Efavirenz, namely Sustiva), Etravirine, trade name Intelence), Nevirapine, called Viramune), Rilpivirine, brand name Edurant)]
3. **Protease Inhibitors (PIs)** : [Atazanavir, (Atazanavir sulfate, ATV) trade name Reyataz), Darunavir, (Darunavir ethanolate, DRV) called (Darunavir ethanolate, DRV), Fosamprenavir, (Fosamprenavir calcium, FOS-APV, FPV)namely Lexiva), ritonavir, brand name Norvir), Saquinavir, (Saquinavir mesylate, SQV) called Invirase), Tipranavir, trade name Aptivus)]
4. **Fusion Inhibitors** : [(Enfuvirtide, trade name

Fuzeon)]

5. **CCR5 Antagonists**: [(Maraviroc , trade name Selzentry)]
6. **Integrase Strand Transfer Inhibitor (INSTIs)** : [(Cabotegravir, (Cabotegravir sodium, CAB) trade name Vocabria), Dolutegravir, (Dolutegravir sodium, DTG), brand name Tivicay), Raltegravir, Raltegravir called Isentress)]
7. **Attachment Inhibitors**: [(Fostemsavir, (Fostemsavir tromethamine, FTR) brand name Rukobia)]
8. **Post-Attachment Inhibitors**: [(ibalizumab-uiyk trade name Trogarzo)]
9. **Pharmacokinetic Enhancers**: [(Cobicistat namely Tybost)]

II. Related Work

This work is focused on identifying what is the most estimated harmful toxin for humans and what is the best approved HIV Medications.

drug likeness evaluation by Lipinski's rules

MW (Molecular weight g/mol) <=500; LogP (Partition Coefficient) <=5; Hacc ((hydrogen bond acceptor)<=10; Hdon ((hydrogen bond donor)<=5 [13].

Biological activity evaluation by Pass Online Antiviral HIV drugs are investigated by PASS ((Prediction of Activity Spectra for Substances) server (http://www.way2drug.com/passonline/).

Three different parameters are evaluated: Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds and Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds and biological activity. It is important to mention that it is necessary to register and provide a Canonical SMILE to predict their predicted function [14].

ADMETlab platform interface for systematic ADMET evaluation

Basic physicochemical property and ADMET properties prediction are: LogS (Solubility in log mol/L), LogD7.4 ((Distribution Coefficient D), LogP ((Distribution Coefficient P), Absorption (Caco-2 (Caco-2 Permeability in cm/s)), Distribution (PPB (Plasma Protein Binding in%) and VD (Volume Distribution in L/kg) Metabolism [(CYP450 1A2 inhibitor), CYP4501A2-substrate),CYP450 3A4 inhibitor,CYP450 3A4, substrate CYP450 2C9 inhibitor, CYP450 2C9 substrate, CYP450 2C19 inhibitor, CYP4502C19 substrate, CYP4502D6 inhibitor,CYP450 2D6 substrate)], Excretion (CL or Clearance in mL/min/kg and T1/2, (Half Life in h)) and Toxicity (LD50 of acute toxicity in -log mol/kg). Six methods (RF, SVM, RP, PLS, NB, DT) and seven types of descriptors (2D, Estate, MACCS, ECFP2, ECFP4, ECFP6, FP2) were applied in the modeling process (https://admet.scbdd.com/home/interpretation/#part3).

Meaning & Preference according to ADMETlab platform

- LogS (The logarithm of aqueous solubility value in log mol/L) Optimal: higher than -4 log mol/L; <10 μg/mL: Low solubility; 10–60 μg/mL: Moderate solubility; >60 μg/mL: High solubility [15].

-LogD7.4 (logarithmic value of n-octanol/water distribution coefficients at pH=7.4. It is Lipophilicity based on pH for ionizable compounds). LogD7.4 < 1: Solubility high; Permeability low by passive transcellular diffusion; Permeability possible via paracellular if MW < 200 g/mol ; Metabolism low; 1 to 3: Solubility moderate; Permeability moderate; Metabolism low 3 to 5: Solubility low; Permeability high; Metabolism moderate to high. > 5: Solubility low; Permeability high; Metabolism high [16].

- LogP (Distribution Coefficient P, that is estimated Lipophilicity): Optimal: 0 < LogP < 3; LogP < 0: poor lipid bilayer permeability; LogP > 3: poor aqueous solubility [17].

- Papp (Caco-2 human colon adenocarcinoma cell lines Permeability, log Papp (log cm/s)): Optimal: higher than -5.15 Log unit or -4.70 or -4.80 [18].

- PPB (Plasma Protein Binding): > 90% Significant with drugs that are highly protein-bound and have a low therapeutic index [19].

- VD (Volume Distribution): Optimal: 0.04-20L/kg; Range:<0.07L/kg: Confined to blood, Bound to plasma protein or highly hydrophilic; 0.07-0.7L/kg: Evenly distributed; >0.7L/kg: Bound to tissue components (e.g., protein, lipid), highly lipophilic [20].

- T 1/2 (The half-life of a drug. T1/2): Range: > 8h: high; 3h< Cl < 8h: moderate; < 3h: low [19].

- CL (The clearance of a drug): Range: > 15 mL/min/kg: high; 5mL/min/kg< Cl < 15mL/min/kg: moderate; < 5 mL/min/kg: low [19].

- LD50 (as known “"lethal dose, 50% “,The rat oral acute toxicity, a median lethal dose (LD50) usually represents the acute toxicity of chemicals. It is the dose amount of a tested molecule to kill 50 % of the treated animals within a given period; High-toxicity: 1~50 mg/kg; Toxicity: 51~500 mg/kg; low-toxicity: 501~5000 mg/kg. [21]

pkCSM server for toxicity evaluation

Herein, several toxicity parameters are performed by pkCSM platform (http://biosig.unimelb.edu.au/pkcsm/), 22 for instance: AMES toxicity; Max. tolerated dose (human) (log mg/kg/day in units); Oral Rat Acute Toxicity (LD50) (mol/kg in units) Oral Rat Chronic Toxicity (LOAEL); Log mg/kg_bw/day in units); Hepatotoxicity; Skin Sensitisation; Pyriformis toxicity (log μg/L)and Minnow toxicity (log mM in units).

III. Results and Discussion

Generally speaking, to evaluate the therapeutic efficacy of drug it must be selective, potent, soluble, with low

toxicity and with an excellent therapeutic index, (a quantitative measurement of the relative safety of a drug) and to be not harmful to the organism, and also to be bioavailable, (an indicator of the efficiency of the drug delivery to the systemic circulation) on the human being. Therefore, an eligible drug usually needs to keep a balance between lipophilicity and hydrophilicity to dissolve in the body fluid and penetrate the bio membrane effectively.

Another topic parameter in the Pharmacology field is therapeutic index which is one of the most important parameter which indicates the Ratio between lethal dose 50 (LD50) and effective dose 50 (DE50): IT = LD50 / DE50. This report aims on the role of HIV drugs, through the use of the ADMETlab platform for the prediction of the pharmacokinetic characteristics of the main drugs used against this viral infection, in order to be able to estimate which of these drugs best meets the optimal characteristics required of an ideal drug.

According to WHO, (https://www.cdc.gov/hiv/basics/livingwithhiv/treatment.html) HIV Drugs are classified in several category for instance: a) Nucleoside reverse transcriptase inhibitors (Didanosine (ddI), Emtricitabine (FTC), Lamivudine (3TC), Stavudine (dT), Zalcitabine (ddC) and Zidovudine (ZDV, AZT); b) HIV Protease inhibitors (Amprenavir (VX-478), Atazanavir sulfate (ATV), Fosamprenavir calcium, Indinavir sulfate (IDV, MK-639), Opinavir and Ritonavir (ABT-378/r), Nelfinavir mesylate (AG1343), Ritonavir (RTV, Norvir, ABT-538) and Saquinavir (SQV, RO 31-8959) c) Non Nucleoside reverse transcriptase inhibitors (Delavirdine mesylate (DLV), Efavirenz (EFV, DMP 266) and Nevirapine (NVP) d) Nucleotide reverse transcriptase inhibitors (Tenofovir disoproxil fumarate (Viread).

In Table 1-2 are present yourself several predicted characteristics of Antiviral drugs evaluated by ADMETlab, for instance:

- Drugs's Optimal values log S (logarithm of aqueous solubility, higher than -4 log mol/L) are: Amprenavir (-3.879 log mol/L), Zidovudine triphosphate (-2.716 log mol/L), Dolutegravir (-3.768 log mol/L), Darunavir(-3.82 log mol/L), Fosamprenavir(-3.761 log mol/L), Stavudine(-1.718 log mol/L), Zalcitabine(-0.886 log mol/L), Lamivudine(-2.084 log mol/L), Didanosine (-1.62 log mol/L), Emtricitabine (-2.15), Nevirapine (-3.505 log mol/L), Raltegravir (-3.439 log mol/L) , Trizivir (-1.517 log mol/L) and Truvada (-2.464 log mol/L), respectively.

- Drugs's Optimal values of log P are $0 < LogP < 3$ (Distribution Coefficient P, that is estimated Lipophilicity), in terms to balance between lipophilicity and hydrophilicity parameters are: Amprenavir (2.226), Combivir (0.155), Dolutegravir (1.353), Darunavir (2.375), Indinavir (2.867), Fosamprenavir(2.52), and Nevirapine(2.651) respectively.

- Drugs's Optimal values log D7.4 (estimated Lipophilicity), considered into range 1 to 3, in which there is also in the same time a Solubility moderate; a Permeability moderate and Metabolism low are: Amprenavir (2.226), Darunavir (2.298), Enfuvirtide (1.46), Fosamprenavir (2.342), Indinavir (2.627), Lopinavir (1.76), Loviride (2.326), Nelfinavir (1.838), Nevirapine (2.016) Rilpivirine (2.674) and Tipranavir (1.821) .

On the subject of Plasma Protein Binding (PPB) values when these scores are > 90% these became significant so drugs are highly protein bound and have at the same time a low therapeutic index (IT). In our case, the best performed medications with the less capability PBB with high IT (Ratio between lethal dose 50 (LD50) and effective dose 50 (DE50) are: Dolutegravir (ca. 75% PPB), Raltegravir (ca. 76% PBB), Entecavir (ca. 17% PBB), Enfuvirtide (ca. 66% ca. 75% PBB), Emtricitabine (ca 6.6% PBB), Lamivudine (ca. 31% PBB), Stavudine (ca. 6.7% PBB) and Zalcitabine (ca. 8% PBB) respectively. While VD (Volume Distribution in terms L/kg units) is comprised in range 0.07-0.7L/kg: Evenly distributed. If it > 0.7L/kg, Bound to tissue components (e.g., protein, lipid), highly lipophilic. From results of Table 1 Lamivudine (0.069 L/kg), Nelfinavir (0.305 L/kg), Rilpivirine (0.32 L/kg) and Vicriviroc (0.351 L/kg) have shown potentiality to be distributed. Unfortunately, no one drugs seem to be bound to tissue components.

Regarding Papp values, (Caco-2 Permeability, in cm/s in units, log Papp (log cm/s)) is other useful estimated parameter. In general, Human colon adenocarcinoma (Caco-2) cell lines are used to estimate drug permeability in vivo due to their morphological and functional similarities**.** According to ADMETlab platform [18] its optimal value occurs when it is higher than -5.15 log units or -4.70 or -4.80. Our case Doravirine (-4.459 log cm/s), Elvitegravir (-4.963 log cm/s), Etravirine (-5.025 log cm/s), Loviride (-4.704 log cm/s), Maraviroc (-4.878 log cm/s), Nevirapine (-4.513 log cm/s) and Vicriviroc (-4.799 log cm/s) reported best scores values.
Moreover, this work aims to carry out a Drug -Likeness evaluation of retroviral Drugs, through Lipinski's rules (See below Table 2).

Generally speaking, this estimation can be defined, as a complex balance of various molecular properties and structural features that determine whether a particular molecule is similar to known drugs. From these results, Didanosine (ddI), Emtricitabine (FTC), Lamivudine (3TC), Zalcitabine (ddC), Nevirapine, Loviride, Trizivir (Aztec or Azidothymidine (AZT) and Truvada (Tenofovir) demonstrated the best features according to the Lipinski's rules [13] ((Molecular weight g/mol) <=500; LogP (Partition Coefficient) <=5; H_{acc} ((hydrogen bond acceptor) <= 10; H_{don} ((hydrogen bond donor)<=5).

In addition, In Table 3 are measured several known toxicity indexes of Antiviral drugs, investigated by

pkCSM server [22] for instance AMES toxicity; Max. tolerated dose (human) (log mg/kg/day in units); Oral Rat Acute Toxicity (LD50) (mol/kg in units)Oral Rat Chronic Toxicity (LOAEL); Log mg/kg_bw/day in units); Hepatotoxicity; Skin Sensitisation; Pyriformis toxicity (log µg/L) and Minnow toxicity (log mM in units).

Regarding, Maximum Tolerated Dose (MTD), describes the highest dose of a radiological or pharmacological treatment that will produce the desired effect without unacceptable toxicity. This parameter commonly estimated as the maximum dose that can be given for the duration of a specific study. Broadly speaking, according to ADMETlab platform for a given compound a MRTD of less than or equal to 0.477 log mg/kg/day is considered low, and high if greater than 0.477 log mg/kg/day. In our own case, Elvitegravir (0.87 log mg/kg/day), Didanosine (0.914 log mg/kg/day), Emtricitabine (1.054 log mg/kg/day), Lamivudine (1.006 log mg/kg/day), Zalcitabine (1.022 log mg/kg/day) and Truvada, brand-name medication formed from a combination of two antiviral medicines (Tenofovir-DF and Emtricitabine (FTC) (0.846 log mg/kg/day) are shown excellent MTD value compared to other estimated medications values. (See Table 3).

The Ames test is a adaptable method for evaluating whether the target compound is mutagenic or not. It can give a positive or negative (mutagenic action) and negative (no mutagenic function) result. In our case (See Table 3), only Didanosine is described as positive value. Rat LD50 (Lethal Assay Values in mol/kg) are a standard measure of acute toxicity. It is the amount of a drug administered all at once that causes 50% of a group of experimental animals to die. From analysis, only three among all investigated HIV drugs are shown the higher toxicity. They are Didanosine (1.742 mol/kg), Emtricitabine (1.761 mol/kg) and Raltegravir (1.707 mol/kg), respectively.

Oral rat Chronic Toxicity are calculated by LOAEL value (Lowest Observed Adverse Effect) in log(mg/kg_bw/day). From predicted this value Maraviroc (0.101 log(mg/kg_bw/day , Etravirine (0.896 log(mg/kg_bw/day) , Rilpivirine (0.672 log(mg/kg_bw/day) and Vicriviroc (-0.082 log(mg/kg_bw/day) have reported the lowest concentration Observed Adverse Effect, rather the other antiviral drugs, proving to be more toxic drugs.

Apropos of, Hepatotoxicity test and Skin Sensitisation respectively, Combivir, drug based on the active ingredient Lamivudine + Zidovudine (named Zidovudine Triphosphate), Enfuvirtide and Loviride they are the only three that did not lead to a liver-damaging effect according to this investigation. As far as Skin Sensitisation no HIV drugs evaluated appears to be affected.

Minnow toxicity (The lethal concentration values, LC50) represents the concentration of a molecule necessary to cause the death of 50% of the Flathead Minnows. If LC50 values below 0.5 mM (log LC50 < 0.3) are considered as high acute toxicity. In our case, Tipranavir (-2.023 log mM), Lopinavir (-1.501 log mM) and Maraviroc (-1.613 log mM) are considered as high acute toxicity. T. Pyriformis toxicity test (pIGC50, negative logarithm of the concentration required to inhibit 50% growth in log µg /L, with a value > -0.5 log µg/L is considered toxic. In our case, only Stavudine has been shown to have a minor toxic effect (-0.011 log µg/L).
Finally in Table 4 Biological activity prediction of Antiviral HIV-Drugs, are evaluated by PASS ONLINE platform [14].

Table 1. Physicochemical Property evaluation and ADMET Prediction properties of Antiviral HIV-Drugs, evaluated by ADMETlab platform

Anti-HIV Drugs	LogS (Solubility)	LogD7.4 (Distribution Coefficient D)	LogP (Distribution Coefficient P)	Papp (Caco-2 Permeability)	PPB% (Plasma Protein Binding)	VD (Volume Distribution)	T 1/2 (Half Life)	CL (Clearance)	LD50 (LD50 of acute toxicity)
Atazanavir	-4.582	3.224	4.212	-5.434	86.582	-0.177	1.972	1.09	3.073
Amprenavir	-3.879	2.226	2.226	-5.736	90.311	-1.156	1.334	1.001	3.187
Cobicistat	-5.2	3.622	6.001	-5.234	81.703	-0.298	1.893	1.002	3.079
Combivir	**-2.716**	**0.133**	**0.155**	**-6.189**	**49.125**	**-1.297**	**1.268**	**0.448**	**2.953**
Darunavir	-3.82	2.298	2.375	-5.83	93.448	-1.228	1.321	0.998	3.239
Dolutegravir	-3.768	0.081	1.353	-5.163	75.022	-0.682	1.192	1.161	2.701
Doravirine	-4.342	1.874	2.655	-4.459	88.756	-0.892	1.384	1.093	2.945
Elvitegravir	-5.107	0.838	4.281	-4.963	95.521	-0.88	1.935	1.316	2.858
Enfuvirtide	-3.346	1.46	-15.378	-6.292	66.25	-0.832	/	-1.02	2.998
Fosamprenavir	-3.761	2.342	2.52	-6.082	85.473	-1.342	1.411	0.826	3.137
Etravirine	-5.811	2.929	4.717	-5.026	91.522	-0.355	1.662	1.245	2.841
Entecavir	-2.258	0.365	-0.828	-5.94	17.382	-0.268	0.717	1.858	1.858
Didanosine	-1.62	-0.247	-0.211	-5.111	11.153	-0.291	0.696	1.934	2.447
Emtricitabine	-2.15	-0.354	-0.455	-5.123	6.645	-0.234	0.972	1.882	2.713
Lamivudine	-2.084	-0.676	-0.594	-5.085	31.439	0.069	1.7	1.635	2.6
Stavudine	-1.718	-0.512	-0.709	-5.196	6.7	-0.465	0.538	1.897	2.008
Zalcitabine	-0.886	-0.557	-0.505	-5.123	7.927	-0.443	0.379	1.734	1.734

Indinavir	-3.8	2.627	2.867	-5.638	88.209	0.602	1.762	1.415	3.551
Lopinavir	**-4.763**	**1.76**	**4.328**	**-5.351**	**97.551**	**-0.189**	**1.863**	**1.364**	**3.042**
Loviride	-5.511	2.326	4.143	-4.704	92.914	-0.533	1.646	1.054	2.554
Maraviroc	-5.831	4.14	5.951	-4.878	89.483	0.538	1.759	1.589	3.261
Nelfinavir	-5.039	1.838	4.748	-5.254	94.791	0.234	1.582	1.23	3.307
Nevirapine	-3.505	2.016	2.651	-4.513	64.183	0.305	1.598	2.076	2.523
Raltegravir	-3.439	-0.252	0.912	-5.338	76.3	-1.092	0.981	1.051	2.554
Rilpivirine	-6.643	2.674	4.989	-5.097	90.855	0.32	2.096	1.788	2.619
Ritonavir	-5.304	3.593	5.905	-5.31	97.537	-0.847	1.868	1.089	3.04
Tipranavir	-5.453	1.821	7.326	-5.272	92.366	-1.049	1.789	0.557	3.55
Trizivir	-1.517	-0.353	-0.196	-5.103	36.44	-0.501	0.649	1.822	2.198
Truvada	-2.464	-0.243	-0.051	-5.556	20.077	-0.329	1.434	1.197	3.415
Vicriviroc	-5.428	3.259	4.501	-4.799	86.313	0.351	1.75	1.148	3.708

Table 2. Druglikeness evaluation through Lipinski's rules of Antiviral HIV-Drugs, evaluated by ADMETlab platform.

Anti-HIV Drugs	**MW (g/mol)**	**logP**	**Hacc (hydrogen bond acceptor)**	**Hdon (hydrogen bond donor)**
Atazanavir	704.869	4.212	9	5
Amprenavir	505.637	2.403	7	3
Cobicistat	776.042	6.001	10	3
Combivir	507.182	0.155	11	5
Darunavir	547.674	2.375	8	3
Dolutegravir	419.384	1.353	6	2
Doravirine	425.754	2.655	7	1
Elvitegravir	447.89	4.281	5	2
Enfuvirtide	4491.945	-15.378	60	63
Fosamprenavir	585.616	2.52	8	4
Etravirine	435.285	4.717	7	2
Entecavir	277.284	-0.828	7	4
Didanosine	236.231	-0.211	6	2
Emtricitabine	247.251	-0.455	7	2
Lamivudine	229.261	-0.594	7	2
Zalcitabine	211.221	-0.505	6	2
Indinavir	613.803	2.867	7	4
Lopinavir	628.814	4.328	5	4
Loviride	351.233	4.143	3	2
Maraviroc	513.677	5.951	5	1
Nelfinavir	567.796	4.748	6	4
Nevirapine	266.304	2.651	4	1
Raltegravir	444.423	0.912	9	3
Rilpivirine	366.428	4.989	6	2
Ritonavir	720.962	5.905	9	4
Stavudine	224.216	-0.709	5	2
Tipranavir	602.675	7.326	6	2
Trizivir	267.245	-0.196	6	2
Truvada	287.216	-0.243	7	3
Vicriviroc	533.639	4.501	6	0

Table.3 toxicity evaluation of Antiviral HIV-Drugs, evaluated by pkCSM server.

Anti-HIV Drugs	**AMES toxicity**	**Max. tolerated dose (human) (log mg/kg/day)**	**Oral Rat Acute Toxicity (LD50) (mol/kg)**	**Oral Rat Chronic Toxicity (LOAEL) Log mg/kg_bw/day)**	**Hepatotoxicity**	**Skin Sensitisation**	**T.Pyriformis toxicity (log ug/L)**	**Minnow toxicity (log mM)**
Atazanavir	No	-0.16	2.665	2.703	Yes	No	0.285	2.005
Amprenavir	No	-0.633	2.177	2.478	Yes	No	0.304	0.598
Cobicistat	No	-0.263	2.794	3.489	yes	No	0.285	3.375
Combivir	**No**	**0.684**	**2.375**	**4.168**	**No**	**No**	**0.285**	**7.025**
Darunavir	No	-0.763	2.107	2.775	yes	No	0.289	0.610
Dolutegravir	No	0.035	1.921	1.393	yes	No	0.301	3.100
Doravirine	No	0.251	2.689	2.124	yes	No	0.303	3.268

Elvitegravir	No	0.87	2.377	1.839	yes	No	0.285	0.339
Enfuvirtide	No	0.438	2.482	21.255	**No**	No	0.285	63.087
Fosamprenavir	No	-0.261	2.204	2.762	yes	No	0.285	1.468
Etravirine	No	0.417	2.873	0.896	yes	No	0.296	0.987
Entecavir	No	0.282	2.315	2.402	yes	No	0.285	2.835
Didanosine	**Yes**	0.914	1.742	1.749	yes	No	0.285	2.103
Emtricitabine	No	1.054	1.761	1.789	yes	No	0.203	2.972
Lamivudine	No	1.006	1.834	1.556	yes	No	0.106	2.843
Zalcitabine	No	1.022	1.809	1.571	yes	No	0.074	2.946
Indinavir	No	-0.358	2.914	1.428	yes	No	0.285	5.061
Lopinavir	**No**	**-0.297**	**2.382**	**5.949**	**yes**	**No**	**0.286**	**-1.501**
Loviride	No	0.583	2.141	1.285	**No**	No	1.009	0.918
Maraviroc	No	-0.962	2.808	0.101	yes	No	0.298	-1.613
Nelfinavir	No	-0.576	2.54	3.911	yes	No	0.287	1.236
Nevirapine	No	-0.167	2.715	0.962	yes	No	0.332	2.214
Raltegravir	No	0.603	1.707	1.562	yes	No	0.286	2.71
Rilpivirine	No	0.103	2.62	0.672	yes	No	0.366	1.319
Ritonavir	No	0.096	2.703	2.231	yes	No	0.285	1.787
Stavudine	No	0.822	2.048	2.177	yes	No	-0.011	3.271
Tipranavir	No	-0.354	2.367	2.326	yes	No	0.286	-2.023
Truvada	No	0.846	2.176	2.358	yes	No	0.285	2.942
Vicriviroc	No	-0.562	2.971	-0.082	yes	No	0.32	0.867

Table 4. Biological activity prediction of Antiviral HIV-Drugs, evaluated by PASS ONLINE platform.

Anti-HIV Drugs	Molecular Formula	Synonyms	Function	PASS ONLINE SERVER
Atazanavir	C38H52N6O7	(Reyataz)	antiretroviral protease inhibitor	Pa (probability "to be active") = 0,679; Pi (probability "to be inactive") = 0,004 Activity= Antiviral
Amprenavir	C25H35N3O6S	Agenerase	HIV protease inhibitor	Pa= 0,747 Pi = 0,004 Activity= Antiviral
Cobicistat	C40H53N7O5S2	Tybost	cytochrome P450 3A (CYP3A) inhibitor	Pa= 0,834 Pi = 0,001 Activity= CYP2C19 inducer
Combivir	C10H16N5O13P3	Zidovudine triphosphate or Azt-TP	combination tablets containing Lamivudine and Zidovudine	Pa= 0,991 Pi = 0,001 Activity= DNA synthesis inhibitor
Darunavir	C27H37N3O7S	Prezista	antiretroviral protease inhibitor	Pa= 0,878 Pi = 0,003 Activity= Antiviral (HIV)
Dolutegravir	C20H19F2N3O5	Tivicay	(HIV) integrase inhibitor	Pa= 0,463 Pi = 0,027 Activity= Heat shock protein 27 antagonist
Doravirine	C17H11ClF3N5O3	Pifeltro	an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI)	Pa= 0,458 Pi = 0,008 Activity= DNA directed RNA polymerase inhibitor
Elvitegravir	C23H23ClFNO5	Vitekta	(HIV-1) integrase strand transfer inhibitor (INSTI)	Pa= 0,522 Pi = 0,023 Activity= Analgesic, non-opioid
Enfuvirtide	C204H301N51O64	Pentafuside	HIV fusion inhibitor	/
Fosamprenavir	C25H36N3O9PS	(Lexiva)	HIV Protease Inhibitor	Pa= 0,789 Pi = 0,004 Activity= Antiviral
Etravirine	C20H15BrN6O	Intelence	a nonnucleoside reverse transcriptase inhibitor	Pa= 0,756 Pi = 0,002 Activity= Cyclin-dependent kinase 6 inhibitor
Entecavir	C12H15N5O3	Baraclude	a guanosine nucleoside analogue	Pa= 0,758 Pi = 0,010 Activity= Immunosuppressant
Didanosine	C10H12N4O3	Videx	a purine nucleoside analogue and reverse transcriptase inhibitor	Pa= 0,932 Pi = 0,003 Activity= Nucleotide metabolism regulator
Emtricitabine	C8H10FN3O3S	Emtriva	a nucleoside analogue and reverse transcriptase inhibitor	Pa= 0,996 Pi = 0,002 Activity= Antiviral
Lamivudine	C8H11N3O3S	Heptovir	a nucleoside analogue	Pa= 0,996 Pi = 0,002

			and reverse transcriptase inhibitor	Activity= Antiviral
Zalcitabine	C9H13N3O3	Dideoxycytidine	a synthetic dideoxynucleoside	Pa= 0,961 Pi = 0,003 Activity= CDP-glycerol glycerophosphotransferase inhibitor
Indinavir	C36H47N5O4	Crixivan	an antiretroviral protease inhibitor	Pa= 0,758 Pi = 0,003 Activity= Antiviral (HIV)
Lopinavir	C37H48N4O5	Aluviran	an antiretroviral protease inhibitor	Pa= 0,802 Pi = 0,014 Activity= CYP3A substrate
Loviride	C17H16Cl2N2O2	R 89439	a non-nucleoside reverse transcriptase inhibitor	Pa= 0,690 Pi = 0,003 Activity= RNA directed DNA polymerase inhibitor
Maraviroc	C29H41F2N5O	Selzentry	a chemokine co-receptor 5 (CCR5) antagonist	Pa= 0,906 Pi = 0,001 Activity= HIV attachment inhibitor
Nelfinavir	C32H45N3O4S	Viracept	an antiretroviral protease inhibitor	Pa= 0,674 Pi = 0,024 Activity= Nicotinic alpha4beta4 receptor agonist
Nevirapine	C15H14N4O	Viramune	a nonnucleoside reverse transcriptase inhibitor	Pa= 0,733 Pi =0,020 Activity= Nicotinic alpha2beta2 receptor antagonist
Raltegravir	C20H21FN6O5	Isentress	an integrase inhibitor	Pa= 0,641 Pi = 0,002 Activity= HIV-1 integrase inhibitor
Rilpivirine	C22H18N6	Edurant	a nonnucleoside reverse transcriptase inhibitor	Pa= 0,906 Pi = 0,005 Activity= Protein kinase inhibitor
Ritonavir	C37H48N6O5S2	Norvir	an antiretroviral protease inhibitor	Pa= 0,602 Pi = 0,005 Activity= Antiviral
Stavudine	C10H12N2O4	sanilvudine	a nucleoside reverse transcriptase inhibitor	Pa= 0,957 Pi = 0,001 Activity= Nucleoside oxidase (H2O2-forming) inhibitor
Tipranavir	C31H33F3N2O5S	Aptivus	antiretroviral protease inhibitor	Pa= 0,850 Pi = 0,003 Activity= Antiviral (HIV)
Trizivir	C10H13N5O4	Azidothymidine or Zidovudine	nucleoside analogue and reverse transcriptase inhibitor	Pa= 0,939 Pi = 0,003 Activity= Antiviral
Truvada	C9H14N5O4P	Tenofovir	an acyclic nucleotide diester analog of adenosine monophosphate.	Pa= 0,949 Pi = 0,001 Activity= Antiviral (Adenovirus)
Vicriviroc	C28H38F3N5O2	SCH-D or SCH 417690	piperazine-based CCR5 receptor antagonist with activity against human immunodeficiency virus	Pa= 0,869 Pi = 0,002 Activity= Chemokine receptor antagonist

IV. Conclusion and Future Scope

Today we are witnessing a great technological advance, which can be a suitable tool for discovering new drugs that have low side effects for human health. In fact, several Server Tools are available, which through Machine Learning Algorithms try to accurately predict which chemical-physical parameters are best suited to the study of drugs.

This study aims to make a comparison of the main chemical, physical and biological characteristics of the drugs currently used against HIV. Although these theoretical results are presented as preliminary data, we are confident that they will be useful to the scientific community in the drug design field and discover similar biological compounds against HIV. In the complex framework of this kind of study this computation investigation meets the need to discover candidates with an excellent characteristics in terms of both toxicity, ADME parameters, and Drug likeness evaluation.

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