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Evaluation of physiochemical and pharmacokinetic ability of some HIV integrase inhibitors using Lipinski's rule of five

Ahanonu Saviour Ugochukwu
Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria

Abstract
Evaluation of physiochemical and pharmacokinetic ability of thirty five integrase inhibitors was carried out to determine the best drug candidates among them. SwissADME an online software was used in this study and the result obtained revealed that three inhibitors with high molecular weight above 500gmol-1 and high Topological polar surface area(TPSA) are unsuitable as drug candidates while compound 3 with the lowest molecular weight and TPSA is considered the best inhibitor for HIV integrase. The result of this study showed that these compounds are excellent inhibitors for HIV-1 Integrase with significant physiochemical properties and are useful for the development of new HIV-1 Integrase drugs.

Keywords: HIV, physiochemical property, inhibitor, integrase

Introduction
Human immunodeficiency virus (HIV) is an infection which remains a public health issue [1]. Since the onset of the HIV epidemic, AIDs is the primary cause of mortality among women in the reproductive age (15-49) and has resulted in about 14 million orphaned children. The HIV/AIDs pandemic was first recognized in the early 1980s as being due to infection by a novel retrovirus termed HIV [2]. Now the increased prevalence of HIV infection has been recorded in all regions of the world and this can be attributed partly to improvements in the longevity of HIV-infected people as a result of increased access to antiretroviral treatment (ART).
Integration is the third stage in the life cycle of HIV and is caused by the enzyme called HIV Integrase. Evidence exists that HIV DNA preferentially integrates into actively transcribed regions of DNA [3]. At this point, there still remain unpaired flanking regions and gaps between the vDNA and the host genome. Since the cell does not recognize this newly inserted DNA as foreign, host DNA repair elements will respond and repair the ends, leading to fully integrated HIV DNA. Integration can be blocked by a class of HIV inhibitors called integrase inhibitors. Integrase Inhibitors are a class of antiretroviral drugs used for the treatment of AIDS that target HIV integrase, an enzyme responsible for integration of viral cDNA into host genome [4]. The physiochemical properties of the integrase inhibitors such as TPSA, molecular weight, hydrogen bond donor, hydrogen bond acceptor, Octanol water partition coefficient, rotatory bonds and number of heavy atoms provide useful information about the compounds which are to be used to develop new HIV integrase drugs. Also, their pharmacokinetic properties are used to determine the rate of absorption, distribution, metabolism and excretion of these compounds from the body. This study confirmed that the compounds are truly capable of blocking the HIV integrase and will help researchers to synthesize other HIV integrase inhibitors with improved activity.

Materials and Methods
The material used in this study was online Swiss ADME software downloaded using the website http://www.swissadme.ch. The structures of the compounds were drawn using Chemdraw version 2010 software package that contains tools to sketch organic molecules. The drawn structures were separately imported to online SwissADME software to calculate their physiochemical properties.

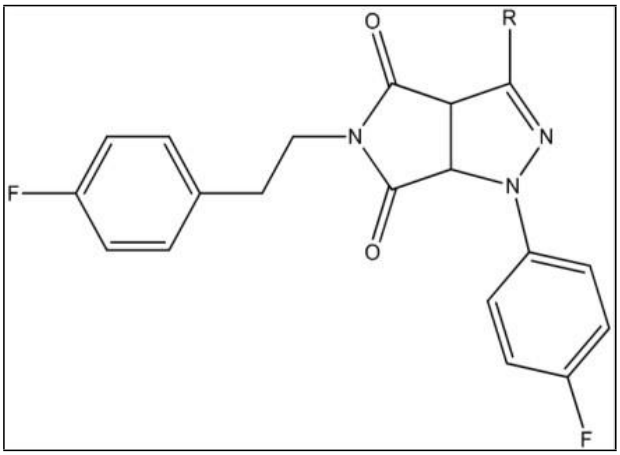

Fig 1

Parent Structure of Integrase Inhibitors
The molecular weight of a compound is one of the physiochemical properties and this depends on the number of heavy atoms present in the compound. It is a measure of absorption, diffusion and distribution of drug in the body. Increase in the number of heavy atoms in the compound increases the molecular weight and this will lead to poor absorption and distribution of drug in the body. Similarly, the excretion of the drug will be slowed down and such will cause toxic to the cells in the body due to its failure to be rapidly excreted from the body.

TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of compounds that gives the information about polarity of compounds [5]. It refers to surface area of oxygen, nitrogen, sulphur attached hydrogen. Poorly absorbed compounds have been identified as those with a TPSA> 140A2 (< 30%) [6]. Hydrogen (H)-bonds are ubiquitous in protein-ligand interactions [7]. Hydrogen bonds are also reported to promote ligand binding affinity by displacing protein-bound water molecules into the bulk solvent.

Too many hydrogen bond donors (NH and OH)/acceptors(C=O) can have a harmful effect on the drug's membrane partition and permeability. Majority of orally active drugs tend to have between five and ten hydrogen bonds. These polar groups can decrease the affinity toward the h upon penetration of the drug. For a drug hydrophobic membrane region and also increase the water desolvation penalty. For a drug to demonstrate favourable pharmacokinetics, a proper balance between lipophilicity and hydrophobicity is very important [8]. Reduced molecular flexibility, as measured by the number of rotatable bonds and low polar surface area or total hydrogen bond count (sum of donor and acceptor) are found to be important predators of good oral bioavailability.

Table 1: Physiochemical properties Four Lipinsk's rule of five (molecular weight, hydrogen bond acceptor, hydrogen bond donor and octanol water partition coefficient) of Integrase inhibitors

Physiochemical Property	Lipinsk's Rule
Molecular weight(gmol-1)	£ 500
Octanol water partition coefficient	£ 5
Number of hydrogen bond donors	£ 5
Number of hyhrogen bond acceptors	£ 10

Table 2: Minimum and maximum physiochemical values of lead compounds for optimum bioavailability

Physiochemical property	Minimum value	Maximum value
Molecular weight	200	500
Log P	-5	5
Hydrogen bond donor	0	5
Hydrogen bond acceptor	0	10
Formal charge	-2	2
Rotatable bond	0	8
Number of heavy atoms	15	50

Results and Discussion

Table 3: Physiochemical properties of Integrase Inhibitors.

Molecule No	Molecular Formula	Molecular Weight(g/ml)	LogP	TPSA (A2)	nrotb	nHBA	nHBD	nHeavy atoms
1.	C25H19F2N3O4	463.43	3.55	93.44	5	7	2	34
2.	C26H21F2N3O4	477.46	3.90	82.44	6	7	1	35
3.	C25H19F2N3O2	431.43	4.28	52.98	5	5	0	32
4.	C25H19F2N3O3	447.43	3.85	73.21	5	6	1	33
5.	C25H19F2N3O4	463.43	3.51	93.44	5	7	2	34
6.	C25H18F3N3O3	465.42	4.16	73.21	5	7	1	34
7.	C25H18F3N3O3	465.42	4.10	73.21	5	7	1	34
8.	C25H18ClF2N3O3	481.88	4.40	73.21	5	6	1	34
9.	C25H18F2N4O5	492.43	3.40	119.03	6	8	1	36
10.	C26H21F2N3O3	451.46	4.18	73.21	5	6	1	34
11.	C26H21F2N3O4	477.46	3.82	82.44	6	7	1	35
12.	C26H21F2N3O4	477.46	3.83	82.44	6	7	1	35
13.	C26H21F2N3O4	477.46	3.83	82.44	6	7	1	35
14.	C27H23F2N3O4	491.93	4.21	82.44	7	7	1	36
15.	C26H20F2N4O6	522.46	3.18	128.26	7	9	1	38
16.	C27H23F2N3O4	481.49	4.20	71.44	7	7	0	36
17.	C26H19F2N3O4	475.44	4.08	71.44	5	7	0	35
18.	C29H21F2N3O3	497.49	4.71	73.21	5	6	1	37
19.	C22H16F2N4O2S	438.45	3.73	94.11	5	6	0	31
20.	C24H18F2N4O2	432.42	3.65	65.87	5	6	0	32
21.	C26H21F2N3O4	477.46	3.83	82.44	6	7	1	35
22.	C26H21F2N3O4	477.46	3.80	82.44	6	7	1	35
23.	C25H19ClFN3O4	493.91	4.19	82.44	6	6	1	35
24.	C26H20F3N3O4	495.45	4.11	82.44	6	8	1	36
25.	C26H20F3N3O4	495.45	4.11	82.44	6	8	1	36
26.	C27H21F4N3O4	527.47	4.56	82.44	7	9	1	38
27.	C26H23FN4O6S	538.55	2.31	150.98	7	9	2	38
28.	C26H22FN3O4	459.47	3.51	82.44	6	6	1	34
29.	C27H24FN3O4	473.50	3.82	82.44	6	6	1	35
30.	C27H24FN3O5	489.49	3.52	91.67	7	7	1	36
31.	C26H21F2N3O4	477.46	3.84	82.44	6	7	1	35
32.	C26H21F2N3O4	477.46	3.83	82.44	6	7	1	35
33.	C26H21ClFN3O4	493.91	4.03	82.44	6	6	1	35

34.	C26H22FN3O4	459.47	3.58	82.44	6	6	1	34
35.	C27H24FN3O5	489.49	3.57	91.67	7	7	1	36

Table 4: Pharmacokinetics of Integrase Inhibitors

No	Molecular Formula	Pharmacokinetics				
		CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1.	C25H19F2N3O4	No	No	No	Yes	No
2.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
3.	C25H19F2N3O2	No	Yes	Yes	No	Yes
4.	C25H19F2N3O3	No	Yes	Yes	No	Yes
5.	C25H19F2N3O4	No	No	Yes	Yes	No
6.	C25H18F3N3O3	No	Yes	Yes	No	No
7.	C25H18F3N3O3	No	Yes	Yes	No	No
8.	C25H18ClF2N3O3	No	Yes	Yes	No	No
9.	C25H18F2N4O5	No	Yes	Yes	No	No
10.	C26H21F2N3O3	No	Yes	Yes	No	Yes
11.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
12.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
13.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
14.	C27H23F2N3O4	No	Yes	Yes	Yes	Yes
15.	C26H20F2N4O6	No	Yes	Yes	Yes	Yes
16.	C27H23F2N3O4	No	Yes	Yes	Yes	Yes
17.	C26H19F2N3O4	No	Yes	Yes	Yes	Yes
18.	C29H21F2N3O3	No	Yes	Yes	No	No
19.	C22H16F2N4O2S	No	Yes	Yes	Yes	Yes
20.	C24H18F2N4O2	No	Yes	Yes	Yes	Yes
21.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
22.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
23.	C25H19ClFN3O4	No	Yes	Yes	Yes	Yes
24.	C26H20F3N3O4	No	Yes	Yes	Yes	Yes
25.	C26H20F3N3O4	No	Yes	Yes	Yes	Yes
26.	C27H21F4N3O4	No	Yes	Yes	No	Yes
27.	C26H23FN4O6S	No	No	Yes	No	Yes
28.	C26H22FN3O4	No	Yes	Yes	Yes	Yes
29.	C27H24FN3O4	No	Yes	Yes	Yes	Yes
30.	C27H24FN3O5	No	Yes	Yes	Yes	Yes
31.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
32.	C26H21F2N3O4	No	Yes	Yes	Yes	Yes
33.	C26H21ClFN3O4	No	Yes	Yes	Yes	Yes
34.	C26H22FN3O4	No	Yes	Yes	Yes	Yes
35.	C27H24FN3O5	No	Yes	Yes	Yes	Yes

Table 2 showed that all the integrase inhibitors do not violate Lipinski's rule except compounds 15, 26 and 27 that have only one violation (molecular weight > 500gmol-1) according to Table 1 above. These compounds have very low oral bioavailability with high TPSA, high molecular weight, flexible bonds and hydrogen donor and acceptor count values.

High Topological polar surface area (TPSA) is caused by increase in hydrogen bond donor and acceptor and results in decrease in permeability [9]. Too many hydrogen bonds can have deleterious effect on drug's membrane partition [10]. These polar groups can decrease the affinity toward the hydrophobic membrane region [11]. All the compounds according to table 2 have number of heavy atoms within an acceptable range of 15 and 50 which enables their easy development into drugs. Log P values of less than 5 means that the affinity for the lipids of an organism is insufficient to exceed the bio- accumulation criterion and it indicates that all the ligands used in this study are not toxic. Compound 3 is the best inhibitor for integrase with low molecular weight, TPSA, number of heavy atoms and sum of hydrogen bond donor and acceptor less than 12. It is easily absorbed, diffused, distributed and excreted causing no harm to the cells in the body. In Table 4, all the compounds are potent inhibitors for at least one cytochrome P450 superfamily of enzymes but they failed to inhibit CYP1A2, an enzyme responsible for the metabolism of caffeine.

Conclusion

This study revealed that, comparing and analysing all the parameters, compound three with the lowest molecular weight and TPSA could be projected as the best potent anti-HIV inhibitor and the most favourable drug candidate. The inhibitors octanol water partition coefficient, hydrogen bond donor and acceptor count are in agreement with Lipinski's rulemaking them to be considered good for drug design. The pharmacokinetic properties of these inhibitors can provide a useful tool to predict the activity of new compounds and also design new compounds with anti-HIV-1 inhibitors activity.

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