Tetrahydroxy Cyclic Urea-Potent Inhibitor for HIV-1 Protease Wild Type and Mutant Type - A Computational Design

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Abstract: A series of novel tetrahydroxy cyclic urea molecules as HIV-1 protease inhibitors were designed using computational techniques. The designed molecules were compared with the known cyclic urea molecules by performing docking studies on six of wild type protein and three mutant protein varieties and calculating their ADME properties. A series of novel molecules were designed by substituting hydrogen at the P_1 / P_1' positions with hydroxyl group increasing the bioavailability these had better ADME properties and binding affinity towards HIV-1 protease. The biological activity of these inhibitors were predicted by a model equation generated by the regression analysis between biological activity ($\log 1/K_i$) of known inhibitors and there combined docking scores from six of the wild type protein docking. The synthetic studies are in progress.

Keywords: Docking, ADME, OPLS-AA, MMFF94s, CU (Cyclic urea), THCU (Tetrahydroxy cyclic urea).

Introduction

AIDS is one of the most serious health problems today. Human immune virus type 1 (HIV-1) is the main causative agent of AIDS. Inhibition of virally encoded protease has been demonstrated to be an effective antiviral drug therapy against HIV-1 infection¹. Several HIV-1 protease inhibitors have been shown to reduce the viral load and increase the number of CD4⁺ lymphocytes in HIV infected patients².

HIV protease inhibitors belong to three different classes as reported in the literature, nonhydrolysable transition state isosteres, similar to renin inhibitors; pseudo symmetrical and C-2 symmetrical compounds³ and nonpeptidic inhibitors⁴. Cyclic ureas have shown good HIV protease inhibition. The cyclic urea classes of inhibitors are designed to displace a unique structural water molecule present in the HIV-1 protease active site⁵. These inhibitors have

the hydroxyl groups and carbonyl oxygen positioned which is an essential factor for high potency. The diols *i.e.*, the hydroxyl groups interact with ASP25/25' and the carbonyl oxygen with ILE50/50'. Amino acid residues like ASP30/30', GLY48/48' and ARG8/8' present in the active site also play an important role in inhibitor binding.

Experimental

Method and software

The computational work was run on a 3.2 GHz Intel Pentium-4 systems. The software⁶ Glide 4.0 was used for protein minimization, grid generation and ligand docking Qikprop 2.5 was used⁷ to calculate the ADME properties of the ligands

Nine crystal structures of HIV-1 protease were downloaded from protein data bank out of which three were mutant variety (Wild type pdb *id*: 1PRO, 1BVG, 1AJX, 1SBG, 1HSG and 2UPJ. Mutant type pdb *id*: 1MER, 1MEU and 1MET)⁸⁻¹⁴. These protein structures were prepared by glide application's protein preparation job. The protein preparation facility consists of two components, preparation and refinement. After ensuring chemical correctness, the preparation component adds hydrogen and neutralizes side chains that are not close to the binding cavity and do not participate in salt bridges. The refinement component performs a restrained impact minimization of the co-crystallized complex, which reorients side-chain hydroxyl groups and alleviates potential steric clashes. It uses the OPLS-AA force field for this purpose and then the active site of the protein was defined and a grid was prepared for each of the protein structure with receptor Vander Waals scaling for the non polar atoms as 0.9 (which makes the protein site "roomier" by moving back the surface of non-polar regions of the protein and ligand. This kind of adjustments emulate to some extent the effect of breathing motions to the protein site it is a kind of giving breathing to the receptor). The ligands were built using maestro build panel and prepared by Lig Prep2.0 application. LigPrep produces the low energy conformer of the ligand using the MMFF94s force field. The ADME properties (required pharmacokinetic properties of viable drug compounds) were calculated by Qikprop 2.5. The lower energy conformations of the ligands were selected and were docked into the grid generated from the nine protein structures using the standard precision docking mode¹⁵. In this docking method the ligands are flexible and the receptor is rigid, except the protein active site has slight flexibility. To include receptor flexibility the ligands were docked into different grid generated for nine protein conformations^{16,17}. The known inhibitors which docked into the six of the wild type protein were selected and a regression analysis was performed by taking the combined docking scores of each ligand. The combined docking scores were calculated by taking the sum of glide score (docking scores) of each ligand from the six docking processes.

Results and Discussion

ADME properties of cyclic urea chosen from literature¹⁸⁻²⁴ with varied range of inhibition constant were calculated (structures shown in Figure 1). The calculated ADME properties showed poor bioavailability. The required pharmacokinetic properties for a viable drug compound are²⁵.

- (i) $150 \leq MW \leq 650$
- (ii) $-1 \leq \text{Log Po/w} \leq 6.5$
- (iii) $\text{Log S} \geq -7$
- (iv) $\text{Pmdck} \geq 5$
- (v) $\text{Log BB} \geq -3$

The first three are based on Lipinski rule of five^{26,27}, molecular weight less than 650, partition coefficient between octanol and water (log Po/w) between -1 and 6.5 and solubility (log S) greater than -7. Pmdck and Log BB parameter tells about the ability of the drug to pass through blood brain barrier which is mandatory for inhibition of HIV infection. The ADME values of known inhibitors are given in Table 1.

Figure 1. Structure of Cyclic urea inhibitors. P₂ and P₁ substitutions provided in Table 1.

Table 1. ADME properties of cyclic urea inhibitors

Compd. No.	P2	P1	M. weight	Log Po/w	Log S	Log BB	Pmdck
CU 1	<i>n</i> -propyl	Benzyl	410.55	5.560	-6.020	-0.549	2174.33
CU 2	<i>n</i> -butyl	Benzyl	438.60	6.341	-6.898	-1.056	2172.22
CU 3	<i>n</i> -hexyl	Benzyl	494.71	7.919	-8.624	-1.454	2172.65
CU 4	<i>i</i> -butyl	Benzyl	438.60	6.134	-6.275	-0.739	2785.55
CU 5	<i>i</i> -pentyl	Benzyl	466.66	6.957	-7.536	-1.058	2183.61
CU 6	<i>i</i> -hexyl	Benzyl	494.71	7.804	-8.618	-1.265	2236.78
CU 7	<i>i</i> -heptyl	Benzyl	522.76	8.603	-9.439	-1.472	2172.64
CU 8	Neo-hexyl	Benzyl	494.71	7.579	-8.009	-0.997	2488.23
CU 9	<i>Iso</i> prenyl	Benzyl	430.54	5.815	-5.989	-0.782	2500.15
CU 10	Cyclo propyl methyl	Benzyl	434.57	5.708	-5.839	-0.911	1637.57
CU 11	Cyclo butyl methyl	Benzyl	462.63	6.245	-6.319	-0.882	1769.91
CU 12	Cyclo pentyl methyl	Benzyl	490.68	6.801	-6.741	-0.825	2043.12
CU 13	<i>m</i> - fluoro benzyl	Benzyl	542.62	7.379	-7.508	-0.776	2556.25

Contd...

CU 14	<i>o</i> - fluoro benzyl	Benzyl	542.62	7.328	-7.231	-0.749	2686.60
CU 15	<i>p</i> - fluoro benzyl	Benzyl	542.62	7.492	-7.693	-0.776	2591.58
CU 16	<i>m</i> - chloro benzyl	Benzyl	575.53	7.895	-8.069	-0.777	2544.90
CU 17	<i>p</i> - chloro benzyl	Benzyl	575.53	7.987	-8.476	0.795	2581.98
CU 18	<i>m</i> - bromo benzyl	Benzyl	664.43	7.890	-7.676	-0.717	2751.75
CU 19	<i>m</i> -methyl benzyl	Benzyl	534.69	7.565	-7.158	-0.718	2757.74
CU 20	<i>m</i> -(tri fluoro methyl) benzyl	Benzyl	642.63	8.446	-8.517	-0.754	2617.90
CU21	<i>p</i> -(tri fluoro methyl) benzyl	Benzyl	642.63	9.039	-10.014	-0.756	3092.61
CU 22	<i>m</i> -(hydroxyl methyl benzyl)	Benzyl	566.69	5.511	-5.376	-1.756	362.72
CU 23	benzimd	Benzyl	618.69	4.426	-6.614	-3.142	5.428
CU 24	methyl cyclopropyl	Benzyl	724.90	7.316	-6.956	-2.439	100.72
CU 25	<i>n</i> -butyl	Benzyl	728.93	7.815	-9.150	-3.228	60.95
CU 26	Babz	Benzyl	824.93	8.476	-10.706	-3.303	32.66
CU 27	Babz	i-butyl	756.90	7.490	-9.883	-3.237	34.08
CU 28	Babz	Cyclo hexyl	808.97	8.117	-10.45	-2.468	68.49
CU 29	Babz	<i>p</i> -hydroxy benzyl	856.93	7.093	-9.389	-4.329	4.02
CU30	Babz	<i>p</i> -methoxy benzyl	884.98	8.530	-10.11	-3.309	35.77
CU 31	Benzyl	<i>p</i> -hydroxy benzyl	538.64	5.671	-6.282	-2.019	147.55
CU 32	Benzyl	<i>p</i> - mehtoxy benzyl	566.69	7.382	-7.557	-0.900	3095.42
CU 33	Benzyl	4-2-hydroxyethoxy benzyl	626.74	6.135	-7.269	-2.760	18.475
CU 34	Benzyl	4-(pyridin-4-ylmethoxy) benzyl	720.86	9.086	-10.386	-2.120	598.66
CU 35	Benzyl	4-(2-morpholin-4-ylethoxy)benzyl	764.95	6.853	-6.682	-0.604	46.45
CU 36	Pyrazole	4-(pyridin-4-ylmethoxy) benzyl	852.99	8.551	-10.77	-3.669	23.606
CU 37	Pyrazole	4-[2-(dimethylamino)ethoxy] benzyl	813.00	6.826	-7.55	-2.197	1.848
CU 38	<i>p</i> -Nitro benzyl	Benzyl	596.63	6.028	-7.178	-2.805	21.937
CU 39	<i>p</i> -Amino benzyl	Benzyl	536.67	5.322	-6.217	-2.318	120.619
CU 40	<i>m</i> -Cyano benzyl	Benzyl	556.66	5.670	-7.401	-2.314	64.322
CU 41	<i>N</i> -pyridin-2-yl-benzamide	Benzyl	746.86	7.337	-9.467	-2.795	91.815

The compound CU 23 the best molecule in the series with $K_i < 0.01$ nM had Pmdck value (5.428) and Log BB value (-3.192) less than required. The best docked compound from the series CU 37, CU 29 and CU 26 with combined docking scores -66.81, -66.74 and -66.2 respectively (Combined dock scores are provided in Table 2) which had good biological activity (K_i in nM range) had high molecular weight, their Log Po/w (6.826, 7.093 and 8.476 respectively) and Log S (-7.55, -9.389 and -10.706 respectively) value were not in the acceptable range. The Pmdck value for CU 37 and CU 29 were also very low, lesser than the acceptable range (1.848 and 4.02). The inhibitors CU 30, CU41, and CU 36 which have good biological activity were also having the lesser bioavailability.

Table 2. Biological activity, combined dock score and predicted activity of known cyclic urea inhibitors.

Compd. No.	Ki in nM*	Biological activity (log 1/ki)	Combined dock score (CDS) wild type	Predicted activity from Eq 2	Combined dock score (CDS) mutant
Cu 1	8	8.09691	-45.49	8.332765	-23.09
Cu 2	1.4	8.853872	-54.85	9.195289	-27.8
Cu 3	4.6	8.337242	-50.87	8.828532	-23.74
Cu 4	49	7.309804	-35.52	7.414029	-20.32
Cu 5	12	7.920819	-52.38	8.967678	-28.94
Cu 6	7	8.154902	-54.29	9.143685	-24.78
Cu 7	30	7.522879	-45.04	8.291297	-26.76
Cu 8	36	7.443697	-35.72	7.432459	-22.83
Cu 9	1.8	8.744727	-47.59	8.52628	-21.4
Cu 10	2.1	8.677781	-43.94	8.189932	-25.39
Cu 11	1.3	8.886057	-54.5	9.163036	-28.29
Cu 12	4.3	8.366532	-41.79	7.99181	-16.77
Cu 13	3	8.522879	-49.33	8.686621	-31.21
Cu 14	34	7.468521	-40.63	7.884916	-23.78
Cu 15	1.4	8.853872	-42.2	8.029591	-27.42
Cu 16	0.89	9.05061	-53.4	9.061671	-33.1
Cu 17	5.2	8.283997	-41.23	7.940206	-30.38
Cu 18	1.4	8.853872	-51.08	8.847883	-31.11
Cu 19	7	8.154902	-45.35	8.319864	-29.43
Cu 20	22	7.657577	-39.91	7.818568	-27.55
Cu 21	51	7.29243	-43.9	8.186246	-26.84
Cu 22	0.14	9.853872	-65.44	10.17116	-36.67
Cu 23	0.01	11	-52.65	8.992559	-30.71
Cu 24	0.34	9.468521	-49.42	8.694914	-17.56
Cu 25	1.3	8.886057	-42.47	8.054472	-8.45
Cu 26	0.024	10.61979	-66.2	10.24119	-25.07
Cu 27	0.3	9.522879	-59.48	9.621943	-25.68
Cu 28	0.29	9.537602	-57.54	9.443172	-24.99
Cu 29	0.035	10.45593	-66.74	10.29095	-17.18
Cu 30	0.026	10.58503	-65.94	10.21723	-21.05
Cu 31	1.1	8.958607	-43.95	8.190854	-8.79
Cu 32	8.6	8.065502	-44.42	8.234164	-29.9
Cu 33	0.76	9.119186	-51.14	8.853412	-25.18
Cu 34	0.84	9.075721	-50.34	8.779692	-25.15
Cu 35	5.9	8.229148	-50.28	8.774163	-9.17
Cu 36	0.071	10.14874	-55.14	9.222012	-14.48
Cu 37	0.061	10.21467	-66.81	10.2974	-5.14
Cu 38	2.8	8.552842	-49.41	8.693993	-28.16
Cu 39	1.1	8.958607	-50.15	8.762184	-28.47
Cu 40	3	8.522879	-52.95	9.020204	-35.57
Cu 41	0.043	10.36653	-61.31	9.790578	-30.55

*Ki values from literature ref 18-24

The new molecules (Tetrahydroxy's) were designed with different substitutions at the P2/P2' positions and substituting the hydrogen at P1/P1' positions with hydroxyl group in order to increase the bioavailability (Structures shown in Figure 2). These molecules were first screened for their drug like properties (ADME are provided in Table 3). These had good bioavailability but because of larger no. of hydroxyl group they showed lesser Pmdck value but were in the acceptable range.

Figure 2. Structures of Tetrahydroxy molecules

Table 3. ADME properties of tetrahydroxy molecules

Compd. No.	P2	P1	M. weight	Log Po/w	Log S	Log BB	Pmdck
OHC1	1	Benzyl	598.70	5.012	-6.499	-3.127	44.583
2	2	Benzyl	624.69	5.927	-6.789	-1.926	398.31
3	3	Benzyl	511.35	4.776	-5.734	-1.124	537.739
4	4	<i>p</i> - Hydroxy benzyl	600.67	5.446	-6.712	-2.934	67.402
5	5	<i>p</i> - Hydroxy benzyl	648.71	5.583	-6.441	-2.365	114.22
6	6	<i>p</i> - Hydroxy benzyl	550.57	2.239	-3.605	-2.603	36.672
7	7	Ethyl	480.47	0.048	-2.611	-2.965	6.10
8	8	Ethyl	514.62	5.412	-5.913	-1.062	1139.62
9	9	Ethyl	638.79	4.801	-5.342	-1.971	394.59
10	10	Ethyl	546.62	2.897	-4.621	-2.200	41.237
11	11	Ethyl	626.75	5.848	-6.226	-1.868	623.77
12	12	Ethyl	604.71	4.090	-5.199	-2.294	226.19
13	13	<i>p</i> - fluoro phenyl	510.53	4.192	-4.753	-1.191	1149.09
14	14	Fluro ethyl	450.48	3.826	-3.936	-1.025	886.761
15	15	Fluro ethyl	510.53	2.574	-3.386	-2.089	107.767

The screened molecules were docked into the nine protein grids. These showed good docking scores compared to known inhibitors. Compound OHC-1, 2, and 4 with combined dock scores -69.87, -63.45, and -68.63, respectively (Table 4) have ADME properties in acceptable range except for compound OHC-1 which has less Log BB value than required, it may be due to presence of amine groups which restricts it from crossing the blood brain barrier.

Table 4. Combined dock score and predicted activity of novel tetrahydroxy molecules

Compd. No.	Combined dock score wild type	Combined dock score mutant type	Predicted activity from Eq 2
OHC 1	-69.87	-34.96	10.57938
2	-63.45	-29.14	9.987779
3	-55.24	-30.82	9.231227
4	-68.63	-42.76	10.46512
5	-48.74	-36.98	8.632252
6	-43.35	-24.31	8.135564
7	-36.77	-29.91	7.529217
8	-49.19	-31.08	8.67372
9	-49.71	-37.98	8.721638
10	-47.48	-26.45	8.516143
11	-56.22	-32.85	9.321534
12	-57.69	-38.79	9.456995
13	-37.33	-25.35	7.580821
14	-37.14	-23.56	7.563312
15	-40.2	-23.56	7.845291

A regression analysis of biological activity ($\text{Log } 1/\text{Ki}$) and combined dock score for known inhibitor was carried out. The correlation coefficient $r = 0.801$ and standard error of the estimate $s = 0.59$, and the following equation is found.

$$\text{Biological activity (Log } 1/\text{Ki)} = -0.09369 \cdot \text{cds} + 4.111861 \quad (1)$$

The inhibitor CU 23 having $\text{Ki} < 0.01$ was taken as an outlier and the regression gave a correlation coefficient $r = 0.8415$ and the standard error of estimate s reduced to 0.506 and following equation was obtained, the scatter plot is shown in Figure 3.

$$\text{Biological activity (Log } 1/\text{Ki)} = -0.09215 \cdot \text{cds} + 4.140861 \quad (2)$$

Figure 3. Scatter plot of biological activity in $\text{log } 1/\text{Ki}$ Vs Combined dock score (CDS)

Biological activities of the new inhibitors were predicted from the equation 2, these compounds which had better ADME properties showed comparable biological activity with that of known inhibitors. Compound OHC -1, 2 and 4 with predicted biological activity 10.579, 9.987 and 10.465 respectively were lower than known inhibitor CU 23 but comparable with CU 37, CU 29, CU 26, and CU 30.

The docking study of these known inhibitors and new molecules on the mutant variety of HIV-1 protease showed varied results. The new molecules showed better binding affinity towards the mutant variety protein. Molecules like OHC 4, 5, 9 and 12 showed better docking scores (-42.76, -36.98, -37.98 and -38.79 respectively) than the already known inhibitors.

Since the ADME properties of the new inhibitors are better than the existing ones and they showed better binding affinity towards the protein, these molecules can be consider for further studies as hit molecules.

Conclusion

From the study of ADME properties of known inhibitors and the newly designed one which showed good bioavailability and from the docking studies performed on both wild type and mutant type protein it can be concluded that the new molecules can be considered as a potent inhibitor of HIV-1 protease. Compound like OHC-1,2, 4, 5, 9 and 12 which have better ADME properties can be taken as best hit molecules and can be considered for further studies like QSAR, synthetic studies and biological activity studies.

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