Science Publications

Universal Journal of Pharmacy and Pharmacology, 2022, 1, 403
www.scipublications.org/journal/index.php/ujpp
DOI: 10.31586/ujpp.2022.403

Research Article

Extended Rule of Five and Prediction of Biological Activity of Peptidic HIV-1-PR Inhibitors

Vishnu Kumar Sahu *, Rajesh Kumar Singh, Pashupati Prasad Singh

Department of Chemistry, Maharani Lal Kunwari Post Graduate College, Balrampur, U.P.271201, India

* Correspondence: Vishnu Kumar Sahu (vishnukr_sahu@rediffmail.com)

Abstract: In this research work, we have applied "Lipinski's RO5" for pharmacokinetics (PK) study and to predict the activity of peptidic HIV-1 protease inhibitors. Peptidic HIV-1-PRIs have been taken from literature with their observed biological activities (OBAs) in term of IC50. The logarithms of the inverse of IC50 have been used as biological end point o(log1/C) in the study. For calculation of physicochemical parameters, the molecular modeling and geometry optimization of all the derivatives have been carried out with CAChe Pro software using semiempirical PM3 method. Prediction of the biological activity of the inhibitors has shown that the best QSAR model is constructed from pharmacokinetic properties, molecular weight and hydrogen bond acceptor. This also proved that these properties play important role to describe the PKs of the drugs. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the compounds of the same series.

Keywords: Lipiniski's RO5; peptidic HIV-1-PRIs; QSAR; PM3

How to cite this paper:
Sahu, V. K., Singh, R. K., & Singh, P. P. (2022). Extended Rule of Five and Prediction of Biological Activity of Peptidic HIV-1-PR Inhibitors. *Universal Journal of Pharmacy and Pharmacology*, *1*(1), 20–42. Retrieved from https://www.scipublications.com/journal/index.php/ujpp/article/view/403

Received: July 14, 2022
Accepted: August 30, 2022
Published: September 01, 2022

1. Introduction

Our body is a wonder machine and is composed of various systems and each system is a complex of various organs and each organ is composed of different tissues and each tissue is composed of same types of cells and uncountable reactions is responsible for vitality of the cell. Optimal function of each organ is regulated by innumerable reactions and each reaction is specific with respect to reactants, reaction conditions, enzymes, co-enzymes, co-factor, etc. Thus, systems and finally our body are also directly and or indirectly affected by these too [1]. When optimal level and function of any above mentioned chemical species is changed this led to abnormal body function. To maintain the normal body function some specific chemicals are required and these chemicals are called medicines [2]. The branch of chemistry which deals with design, development, mode of action, effect, side effects, etc. is known as medicinal chemistry. Medicinal chemist was, is, and will be play important role in design and development of drugs of maximum efficiency and no or minimum side effects along with low cost and minimum efforts [3]. The time course of drugs and their effects in the body is mathematically quantified by pharmacokinetics (PKs) study. PKs include absorption (A), distribution (D), metabolism (M), excretion (E) and toxicity (T) of drugs i.e., ADMET. Designing of an appropriate drug regimen is based on these ADMET parameters [4]. Lipiniski states that most "drug-like" molecules have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5. Molecules violating more than one of these rules may have problems with bioavailability [5-9]. The rule is called "Rule of 5", because the border values are 5, 500, 2 × 5, and 5. In this research work, first of all we have applied Lipiniski's rule of five (RO5) in extended form on peptidic HIV-1 protease inhibitors (peptidic HIV-1-PRIs) for PKs study. And secondly, prediction of the activity of the inhibitor has also been made using these PKs properties as descriptors.

2. Materials and methods

The study materials of the present research work are a series of fifty one urea isostere derivatives as peptidic HIV-1-PRIs listed in Scheme-1 [10]. Out of fifty one compounds under study, the 18 compounds (compound no. 1-18) have the parent skeleton of Figure 1A, out of the remaining thirteen, the seventeen compounds (compound no. 19-35) have the parent skeleton of Figure 1B, while the remaining sixteen compounds (compound no. 36-51) have the parent skeleton of Figure 1C. These inhibitors have been taken from literature with their observed biological activities (OBAs) in term of IC_{50} (the concentration of compound leading to 50% effect and expressed in mol L^{-1} or mol g^{-1}) [11,12]. The logarithms of the inverse of IC_{50} have been used as biological end point (log1/C) in the study. For calculation of physicochemical parameters, the molecular modeling and geometry optimization of all the compounds have been carried out with CAChe Pro software using semiempirical PM3 method [13]. The molecular mass of the each compound was calculated by internal procedure from the molecular formula. The log P of each compound was calculated by atom-typing scheme of Ghose and Crippen [14]. The number of hydrogen bond donors in each compound was counted by counting the sum of NH and OH groups while the number of hydrogen bond acceptors in each compound was counted by counting the sum of N and O atoms from their structure formula [15,16].

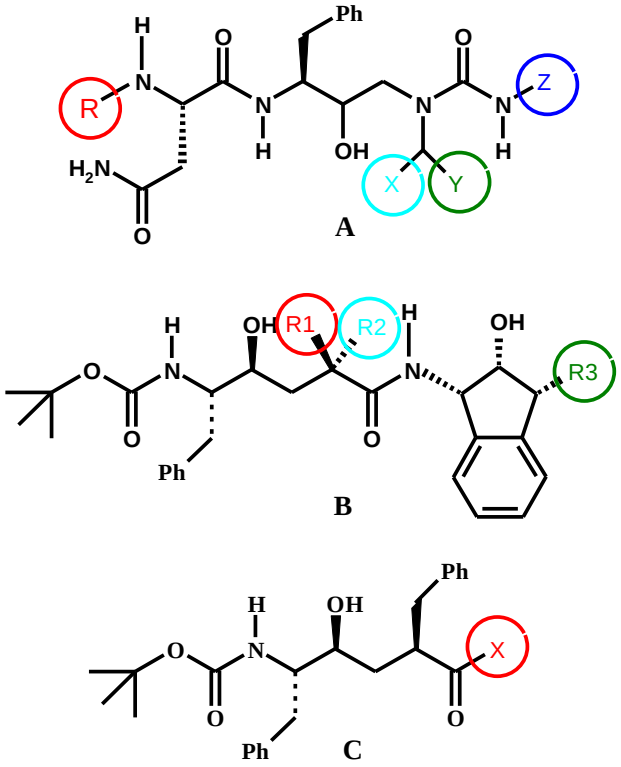


Figure 1. Parent skeleton of peptidic HIV-1-PRIs

3. Results and discussion

Lipinski exposed that RO5 was associated with 90% of orally active drugs that achieved phase-II status [5-9] and this help to reduce attrition during clinical development [17,18]. Veber et al. (2002) extended Lipinski's RO5 by adding fifth and sixth rules that is most drug like molecules have the sum of H-bond donors and acceptor (HD + HA) ≤ 12 and the number of rotatable bond (Rot.Bond) ≤ 10, respectively (Figure 2) [19]. Graphical representation of above criteria for each compound under study has been drawn and is presented in Scheme 2. It was found that molecules violating these rules also show poor oral bioavailability.

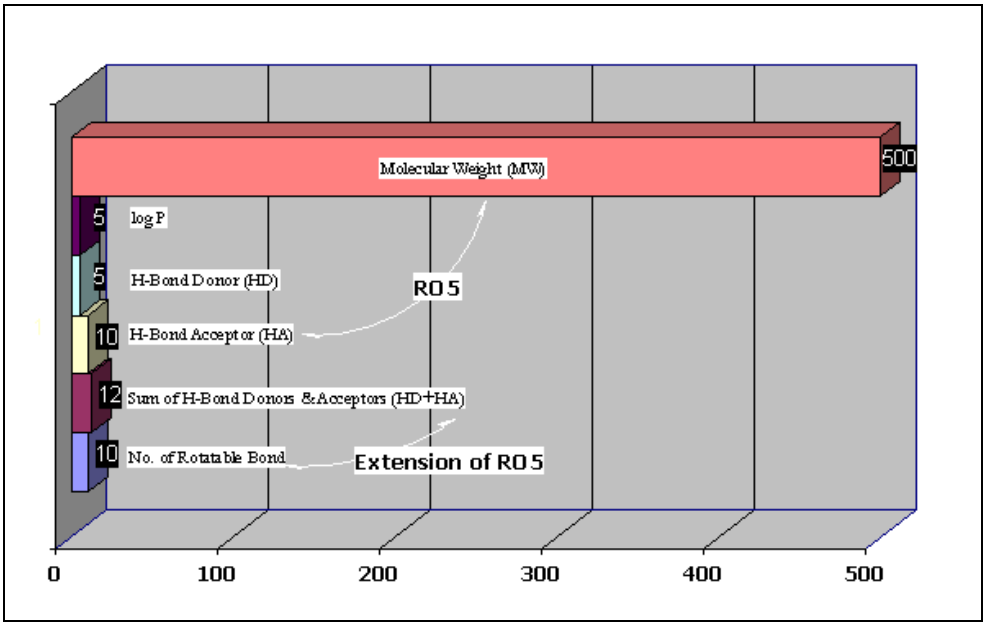


Figure 2. Graphical representation of Lipinski's RO5 with extension

3.1. Molecular Weight (Criteria-1)

Absorption of a drug in our body takes place from intestinal epithelium to blood vessel and from there to action point. It was experimentally scaled that drugs having molecular weight higher than 500Da show a decrease in absorption [7, 20]. The molecular mass of the each compound was calculated by internal procedure from the molecular formula and has been presented in Table 1. A reference to data reveals that compound no. **28**, **30** and **37** follow criteria-1. These compounds have molecular mass less than 500Da while the rest of the compounds have molecular mass greater than 500Da ranging from 502 to 670Da. Drug candidates that disobey criteria-1 are likely to have low solubility and to only pass through cell membranes with difficulty [21]. Thus, out of fifty one compounds, only three compounds: compound no. **28**, **30** and **37**, have reliable solubility and to pass through cell membranes.

Table 1. Values of pharmacokinetic descriptors with observed biological activity of inhibitors

No.	Descriptors						o(log1/C)
	MW	log P	HD	HA	HD+HA	Rot. Bond	
1	541.65	1.79	6	11	17	19	5.82
2	583.73	3.00	6	11	17	22	6.03
3	604.75	3.00	6	11	17	20	6.90
4	569.70	2.60	6	11	17	21	6.29
5	555.67	2.13	6	11	17	20	6.48
6	569.70	2.55	6	11	17	21	6.59
7	583.73	2.62	6	11	17	22	7.46
8	604.75	2.62	6	11	17	20	8.22
9	597.75	3.02	6	11	17	23	7.89
10	618.78	2.95	6	11	17	21	8.52
11	623.79	3.31	6	11	17	20	7.54
12	644.81	3.31	6	11	17	18	8.30

13	617.74	3.19	6	11	17	20	7.72
14	638.77	3.19	6	11	17	18	8.52
15a	631.77	3.6	6	11	17	21	5.19
16a	631.77	3.6	6	11	17	21	5.29
17	618.73	1.88	6	12	18	20	6.98
18	639.75	1.88	6	12	18	18	7.72
19	544.69	5.39	4	7	11	17	9.60
20	558.72	6.05	4	7	11	18	8.11
21	574.72	5.16	5	7	12	19	9.72
22	612.69	6.27	4	8	12	18	9.59
23	570.73	5.92	4	7	11	18	9.64
24	634.64	6.09	4	7	11	17	9.22
25	558.72	5.34	4	9	13	18	9.57
26a	559.70	4.61	6	8	14	18	9.51
27a	589.69	5.34	4	9	13	18	9.57
28	454.57	3.21	4	7	11	15	5.53
29a	560.69	5.1	5	8	13	18	9.8
30	494.63	4.35	2	7	9	17	7.56
31a	670.59	6.65	2	7	9	17	9.14
32	572.70	4.46	2	8	10	18	8.27
33	545.68	4.08	2	7	9	17	9.28
34	576.75	5.18	2	7	9	18	9.60
35	600.80	7.02	2	7	9	21	9.77
36	502.65	5.71	3	6	9	17	6.94
37	494.63	4.24	3	7	10	17	8.02
38	528.69	6.16	3	6	9	16	7.47
39a	546.71	5.59	4	7	11	20	6.16
40	512.65	4.88	4	8	12	21	6.79
41a	586.73	5.66	3	8	11	18	7.18
42a	558.72	5.47	4	7	11	18	6.67
43	510.67	4.75	4	7	12	17	6.91
44	558.72	5.78	4	7	12	17	9.16
45a	560.69	4.98	4	8	12	17	9.75
46	560.69	4.98	4	8	12	17	7.39
47a	508.70	5.83	3	6	9	17	4.52
48	528.69	6.01	3	6	9	16	6.89
49	522.73	6.24	3	6	9	18	6.84
50a	560.69	4.76	5	8	13	18	10.00
51	532.68	5.34	4	7	11	19	7.41

[a] Data points not included in deriving regression equation

3.2. Log P (Criteria 2)

Limit for lipophilicity is log P ≤ 5. The log P of each compound was calculated by atom-typing scheme of Ghose and Crippen and is presented in Table 1 [14]. A reference to these data reveal that compound no. **1**-**18**, **26**, **28**-**30**, **32**, **33**, **37**, **40**, **43**, **45**, **46** and **50** follow criteria-2, while compound no. **19**-**25**, **27**, **31**, **34**-**36**, **41**, **42**, **44**, **47**-**49** and **51** disobey criteria-2 are likely to be poorly soluble in aqueous solution and hence unable to gain access to membrane surfaces [5, 7]. Thus, out of fifty one compounds, only twenty one compounds: compound no. **1**-**18**, **26**, **28**-**30**, **32**, **33**, **37**, **40**, **43**, **45**, **46** and **50**, have reliable lipophilicity and hence able to gain access to membrane surfaces. If a compound is too

hydrophobic (log P >>5), it will remain in the first membrane it contacts and if it is too hydrophilic, it will never cross cell membranes to get to its site of action [22-24].

3.3. Hydrogen bonding

The numbers of hydrogen bond donors and acceptors are known to affect the physicochemical properties (solubility, adsorption, distribution) of a molecule and hence the efficacy of a drug. RO5 states that for better permeation and absorption, the number of donors and acceptors in a ligand should be less than 5 and 10, respectively [25].

3.4. H-bond Donors (Criteria 3)

The number of hydrogen bond donors in each compound was counted by counting the sum of NH and OH groups from their structure formula and is also presented in Table 1 [15]. A reference to these data reveals that compound no. **1**-**18** and **26** disobey criteria-3, while compound no. **19**-**25** and **27**-**51** follow criteria-3. Thus, out of fifty one compounds, only thirty two compounds: compound no. **19**-**25**, and **27**-**51**, have reliable polarity for better permeation and absorption.

3.5. H-bond Acceptors (Criteria 4)

The number of hydrogen bond acceptors in each compound was counted by counting the sum of N and O atoms from their molecular formula and is also presented in Table 1 [16]. A reference to these data reveals that compound no. **1**-**18** disobey Criteria 4, while compound no. **19**-**51** follow criteria-4. Thus, out of fifty one compounds, only thirty three compounds: compound no. **19**-**51**, have reliable polarity for better permeation and absorption. Drug candidates that disobey criteria-3 and or 4 are likely to be too polar to pass through cell membranes [26].

3.6. Sum of H-bond donors and acceptors (Criteria 5)

The number of HD+HA in each compound was counted by counting the sum of HD and HA and is also presented in Table 1. A reference to these data reveals that compound no. **1**-**18**, **26**, **27**, **29** and **51** disobey criteria-5, while compound no. **19**-**25**, **28**, **30**-**49** and **50** follow criteria-5. Thus, out of fifty one compounds, only thirty two compounds (compound no. **1**-**18**, **26**, **27**, **29** and **51**) have reliable polarity for better permeation and absorption [18].

3.7. Number of Rotatable Bonds (Criteria 6)

Rotatable bond (Rot.Bond) is defined as any single non-ring bond, bounded to non-terminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier. This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [18]. The percentage of the dose reaching the circulation is called the bioavailability. The number of Rot.Bond in each compound is also presented in Table 1. A reference to these data reveals that all the compounds disobey criteria-6 as the Rot.Bond is beyond the limits. Thus, all these compounds show poor oral bioavailability of drugs.

The above study indicates that compound no. **1**-**18** obey only criteria-2 and disobey criteria-1, 3, 4, 5 and 6. Compound no. **19**-**25**, **31**, **34**-**36**, **38**, **39**, **41**, **42**, **44**, **47**-**49** and **51** obey criteria-3, 4 and 5 but disobey criteria-1, 2 and 6. Compound no. **26** obeys criteria-2 and 4, while compound no. **27** obeys only criteria-3. Compound no. **29** obeys criteria-3 and 4. Compound no. **50** obeys criteria-2 to 4. Compound no. **28** (OBA=5.53), **30** (OBA=7.56) and **37** (OBA=8.02) obey criteria-1 to 5 and only disobey criteria-6. Compound no. **32**, **33**, **40**, **43**, **45** and **46** obey criteria-2 to 5 but disobey criteria-1 and 6. Thus, out of fifty one peptidic HIV-1-PRIs only three (Compound no. **28**, **30** and **37**) obey above criteria except criteria-6. Thus, the clinical development of peptide-derived compounds has been hindered by

their poor PKs, including low oral bioavailability and rapid excretion and complex and expensive synthesis as concluded by earliest researchers [27-29].

3.8. Prediction of Activity

From the above study, we have observed that out of fifty one peptidic HIV-1-PRIs only three (Compound no. **28**, **30** and **37**) obey above criteria except criteria-6. All physicochemical parameters examined in this study well describe the PKs of the drugs. Taking these observations, we have selected, MW, log P, HD, HA, HD+HA and Rot.Bond, as PK descriptors to predict the activity of the peptidic HIV-1-PRIs. For prediction of the activity of the peptidic HIV-1-PRIs, QSAR model have been developed [30]. In developing QSAR models, MW, log P, HD, HA, HD+HA and Rot.Bond used as independent variables and the log1/C values as dependent variable. Multiple linear regression analysis has been made by Project Leader software associated with CAChe, using the above descriptors (Table 1) in different combinations as described in our previous work [31]. A large number of models were developed, but only top five models are reported here (Eqs.1-5). The predicted activities p(log1/C) as obtained Eqs.1-5 are incorporated in the Table 2. The reliability of these models is very clear from their reliable values of correlation coefficient r^2 and cross-validated correlation coefficient r^2_{CV}. The trends of observed and predicted activities are presented in Figure 3 in the form of correlation matrix plot, while the normal probability plots of residuals in Figures. 4, 5, 6, 7 and 8.

Table 2. Predicted activities of the compounds as obtained by Eqs.1-5.

No.	o(log1/C)	p(log1/C)				
		Eq.1	Eq.2	Eq.3	Eq.4	Eq.5
1	5.82	5.96	6.27	6.26	6.22	6.21
2	6.03	7.03	7.08	7.08	7.15	7.15
3	6.90	7.57	7.54	7.53	7.53	7.52
4	6.29	6.67	6.81	6.80	6.84	6.84
5	6.48	6.32	6.54	6.54	6.54	6.54
6	6.59	6.67	6.81	6.81	6.85	6.85
7	7.46	7.03	7.11	7.11	7.21	7.21
8	8.22	7.57	7.57	7.56	7.58	7.58
9	7.89	7.39	7.38	7.38	7.51	7.52
10	8.52	7.92	7.84	7.84	7.90	7.91
11	7.54	8.05	7.92	7.92	7.91	7.91
12	8.30	8.58	8.38	8.38	8.29	8.28
13	7.72	7.90	7.80	7.80	7.79	7.79
14	8.52	8.43	8.26	8.26	8.17	8.16
15a	5.19	7.91	7.91	7.91	7.91	7.91
16a	5.29	7.91	7.91	7.91	7.91	7.91
17	6.98	7.39	7.44	7.45	7.43	7.44
18	7.72	7.93	7.90	7.91	7.81	7.81
19	9.60	8.15	8.07	8.05	8.04	8.01
20	8.11	8.51	8.32	8.30	8.32	8.29
21	9.72	8.92	8.71	8.67	8.83	8.80
22	9.59	9.35	8.98	8.97	8.93	8.91
23	9.64	8.81	8.59	8.57	8.61	8.58
24	9.22	10.44	9.97	9.95	9.98	9.96
25	9.57	8.24	8.07	8.07	7.96	7.95

26a	9.51	7.86	7.86	7.86	7.86	7.86
27a	9.57	7.99	7.99	7.99	7.99	7.99
28	5.53	5.86	6.29	6.27	6.22	6.18
29a	9.8	7.88	7.88	7.88	7.88	7.88
30	7.56	6.88	7.14	7.14	7.12	7.12
31a	9.14	10.43	10.43	10.43	10.43	10.43
32	8.27	8.34	8.33	8.34	8.35	8.36
33	9.28	8.18	8.27	8.27	8.32	8.32
34	9.60	8.97	8.85	8.85	8.91	8.92
35	9.77	9.58	9.22	9.23	9.34	9.35
36	6.94	7.61	7.66	7.63	7.65	7.62
37	8.02	6.88	7.11	7.10	7.11	7.09
38	7.47	8.27	8.19	8.16	8.13	8.09
39a	6.16	8.06	8.06	8.06	8.06	8.06
40	6.79	6.81	6.93	6.91	7.01	7.00
41a	7.18	8.38	8.38	8.38	8.38	8.38
42a	6.67	8.29	8.29	8.29	8.29	8.29
43	6.91	7.29	7.39	7.55	7.37	7.57
44	9.16	8.51	8.34	8.52	8.31	8.51
45a	9.75	7.88	7.88	7.88	7.88	7.88
46	7.39	8.03	7.96	7.95	7.89	7.87
47a	4.52	7.78	7.78	7.78	7.78	7.78
48	6.89	8.27	8.20	8.18	8.15	8.12
49	6.84	8.12	8.05	8.03	8.08	8.05
50a	10.00	7.88	7.88	7.88	7.88	7.88
51	7.41	7.85	7.82	7.79	7.88	7.85

[a] Data points not included in deriving regression equation

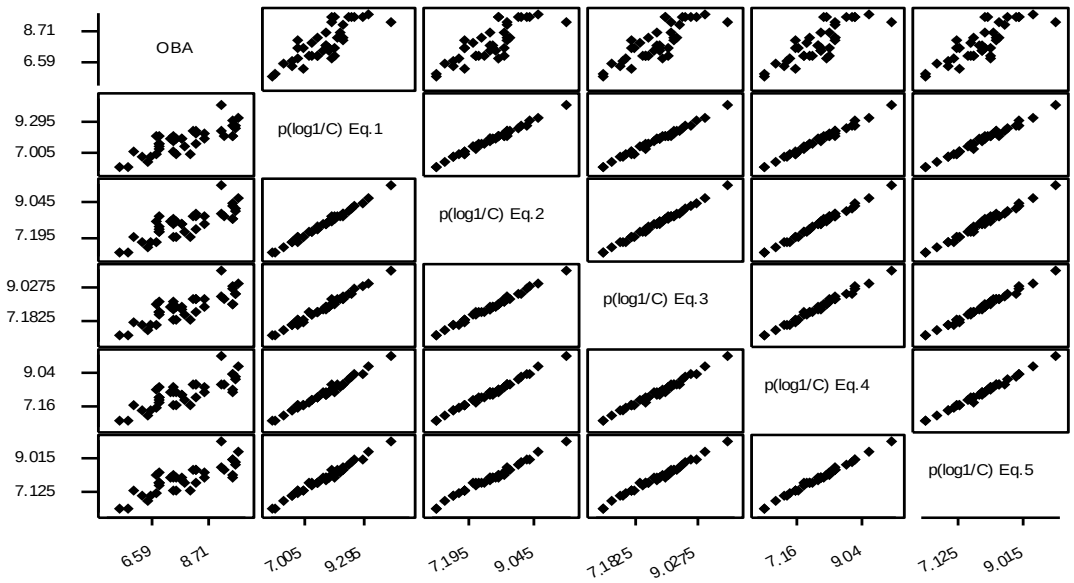


Figure 3. Correlation matrix plot between predicted activities p(log1/C) and observed biological activities log1/C (OBA) of peptidic HIV-1 protease inhibitors.

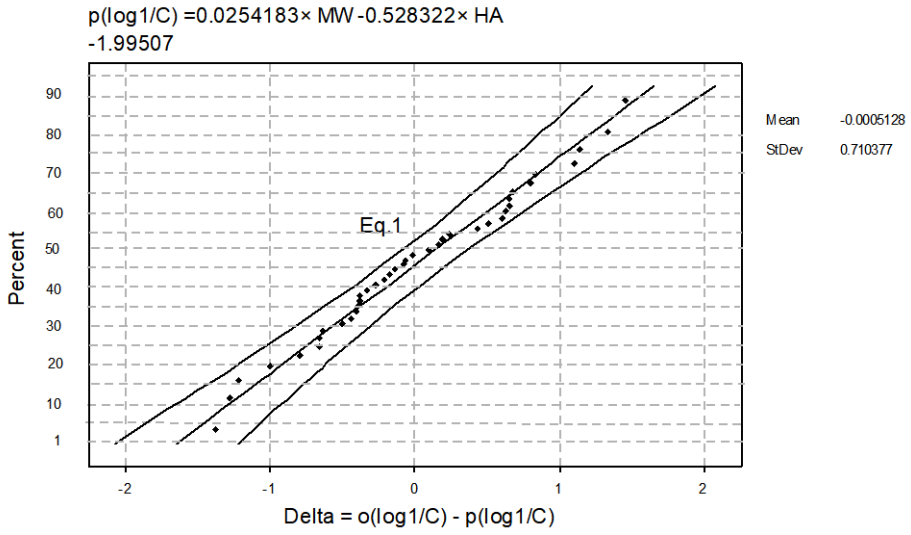


Figure 4. Normal probability plot of residual from Eq. 1

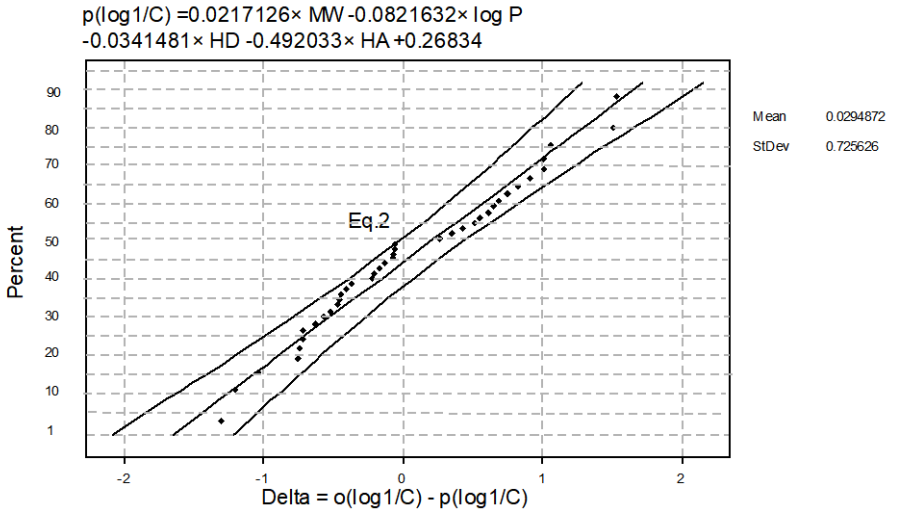


Figure 5. Normal probability plot of residual from Eq. 2

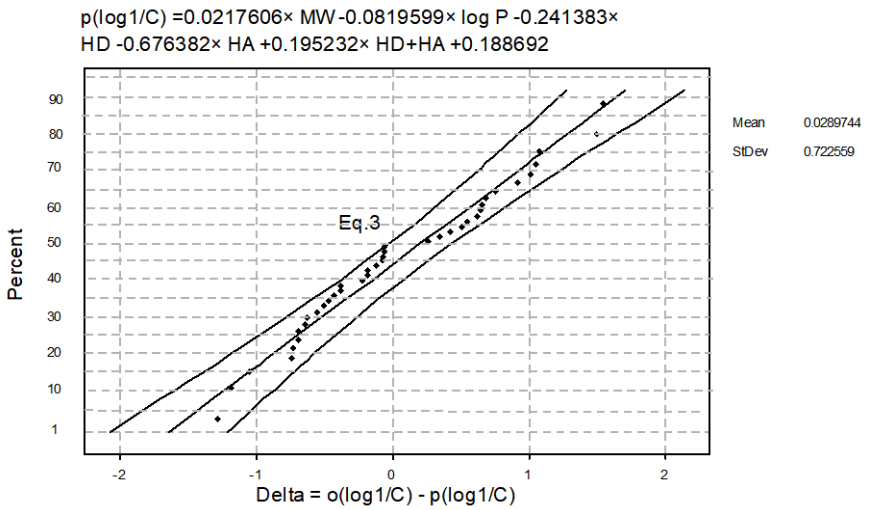


Figure 6. Normal probability plot of residual from Eq. 3

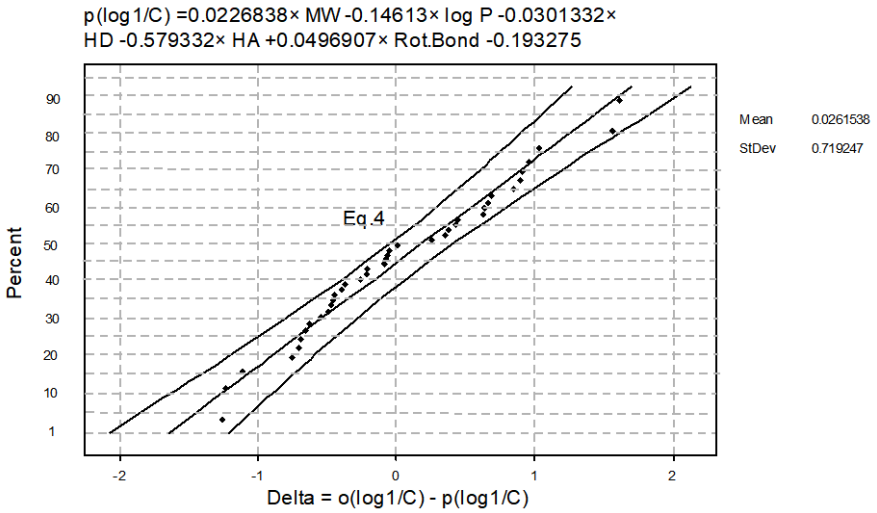


Figure 7. Normal probability plot of residual from Eq. 4

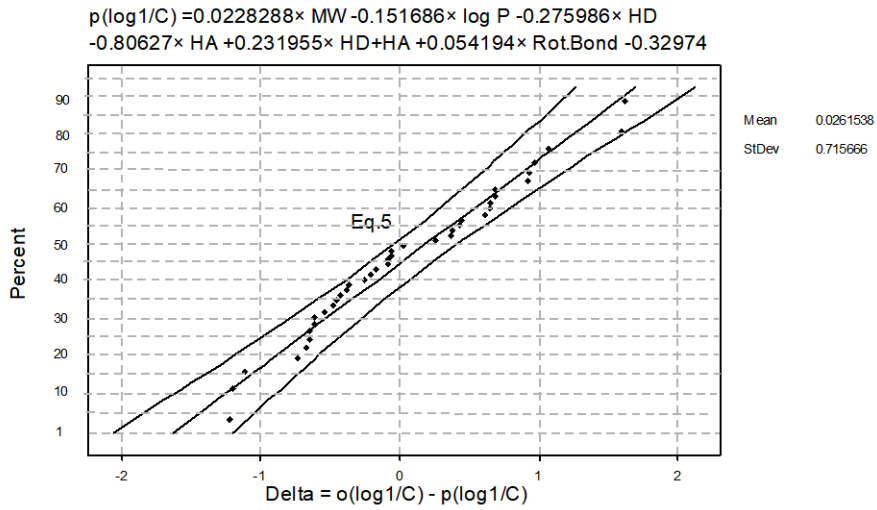


Figure 8. Normal probability plot of residual from Eq. 5

p(log1/C) =0.0254183× MW -0.528322× HA -1.99507
r^2=0.646, r^2_{CV} =0.616, n =39, k =2, df =36, Eq.1
p =0.000, f =26.86

p(log1/C) =0.0217126× MW -0.0821632× log P -0.0341481× HD -0.492033× HA +0.26834
r^2=0.541, r^2_{CV} =0.407, n =39, k =4, df =34, Eq.2
p =0.000, f = 13.87

p(log1/C) =0.0217606× MW -0.0819599× log P -0.241383× HD -0.676382× HA +0.195232× HD+HA +0.188692
r^2=0.542, r^2_{CV} =0.377, n =39, k =5, df =33, Eq.3
p =0.000, f = 10.89

p(log1/C) =0.0226838× MW -0.14613× log P -0.0301332× HD -0.579332× HA +0.0496907× Rot.Bond -0.193275 Eq.4

r^2=0.543, r^2_{CV} =0.380, n =39, k =5, df =33,

p =0.000, f =10.80

p(log1/C) =0.0228288× MW -0.151686× log P -0.275986× HD -0.80627× HA +0.231955× HD+HA +0.054194× Rot.Bond -0.32974 Eq.5

r^2=0.545, r^2_{CV} =0.270, n =39, k =6, df =32,

p =0.000, f =8.84

In the above QSAR models, Eq.1 is best model. The descriptors of the model are MW (molecular weight) and HA (hydrogen bond acceptor), the correlation coefficients and cross-validation are 0.646 and 0.616, respectively, and the predicted activity is presented in Table 2. The best model has been selected on the basis of values of correlation coefficient (r^2) followed by other statistical parameters as shown above.

4. Conclusions

All physicochemical parameters examined in this study well describe the PKs of the drug. Prediction of the biological activity of the inhibitors has shown that the best QSAR model, "p(log1/C) =0.0254183×MW -0.528322×HA -1.99507", is constructed from PK properties, molecular weight and hydrogen bond acceptor. This also proves that these properties are the prerequisite to describe the PKs of the drugs. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the compounds of the same series.

Acknowledgements

The paper is dedicated to Late (Sri) B. P. Sahu on 18th anniversary of his death. The authors gratefully acknowledge the financial support (Project No: C.S.T./D.3564 /11/2009) given by "Council of Science & Technology, U.P., INDIA". One of us (V.K.S.) also thanks U.P.C.S.T., Lucknow, INDIA, for providing research assistantship.

References

[1] Williams DA, Lemke TL (2002) Physicochemical and Biopharmaceutical Properties of Drug Substances and Pharmacokinetics; chapter 7, Principles of Drug Discovery; part 1, Foye's Principles of Medicinal Chemistry 5th edn. pp 115-142, ISBN: 978-0-683-30737-5.

[2] Williams DA, Lemke TL (2002) Drug Design and relationship of Functional Groups to Pharmacologic Activity; chapter 2, Principles of Drug Discovery; part 1, Foye's Principles of Medicinal Chemistry 5th edn. pp 37-67, ISBN: 978-0-683-30737-5.

[3] Voet D, Voet J (2004) Enzymatic Catalysis, Chapter 15, Section 15-4. Drug Design, Biochemistry 3rd Edition, Wiley International Edition. pp 528-546. ISBN: o-471-19350-x(cloth).

[4] Norinder U, Bergstrom CAS (2006) Prediction of ADMET Properties. Chem. Med. Chem., 1, 920 – 937. DOI: 10.1002/cmdc.200600155.

[5] Lipiniski CA, Lombardo F, Dominy BM, Feeney PJ (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliver Rev. 23, 3-25. http://www.ncbi.nlm.nih.gov/pubmed/11259830

[6] Lipinski CA, (2000) Drug-like properties and the causes of poor solubility and poor permeability, Journal of Pharmacological and Toxicological Methods, 44(1), 235-49. http://www.ncbi.nlm.nih.gov/pubmed/11274893

[7] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 46:3-26. http://www.ncbi.nlm.nih.gov/pubmed/11259830

[8] Lipinski CA, (2003) Chris Lipinski discusses life and chemistry after the Rule of Five, Drug Discovery Today, 8(1), 12-16. DOI: 10.1016/S1359-6446(02)02556-4

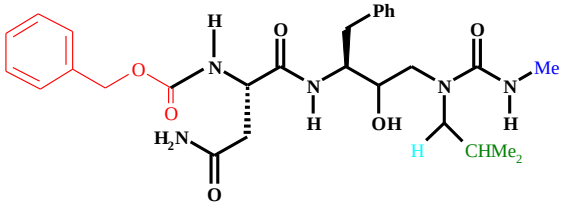
[9] Lipinski CA (2004) Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today: Technologies 1 (4), 337-341. DOI: 10.1016/j.ddtec.2004.11.007.
[10] Garg R, Gupta SP, Gao H, Babu MS, Debnath AK, Hansch C (1999) Comparative Quantitative Structure−Activity Relationship Studies on Anti-HIV Drugs. Chem. Rev. 99: 3525-3602. http://pubs.acs.org/doi/abs/10.1021/cr9703358
[11] Getman DP, DeCrescenzo GA, Heintz RM, Reed KL, Talley JJ, Bryant ML, Clare M, Houseman KA, Marr JJ (1993) Discovery of a novel class of potent HIV-1 protease inhibitors containing the (R)-(hydroxyethyl)urea isostere. J Med Chem 36 (2): 288–291. DOI: 10.1021/jm00054a014.
[12] Holloway MK, Wai JM, Halgren TA, Fitzgerald PMD, Vacca JP, Dorsey BD, Levin RB, Thompson WJ, Chen LJ (1995) A priori prediction of activity for HIV-1 protease inhibitors employing energy minimization in the active site. J. Med. Chem. 38 (2), 305-317. DOI: 10.1021/jm00002a012.
[13] Stewart JJP (1989) Optimization of parameters for semiempirical methods I. Method. J Comput Chem 10(2): 209. DOI: 10.1002/jcc.54010020821.
[14] Ghose AK, Crippen GM (1986) Atomic physicochemical parameters for 3-dimensional structure-directed quantitative structure-activity-relationships. 1. partition-coefficients as a measure of hydrophobicity. J Comput Chem 7: 565-577. DOI: 10.1002/jcc.540070419.
[15] Platts JA (2000) Theoretical prediction of hydrogen bond donor capacity. Phys. Chem. Chem. Phys., 2, 973-980. DOI: 10.1039/a908853i.
[16] Alkorta I, Elguero J (2003) Hydrogen bond acceptor properties of two radicals: nitric oxide molecule and hydrogen atom. ARKIVOC (xiv), 31-36. ISSN 1551-7012.
[17] Smith DA, van de Waterbeemd H (1999) Pharmacokinetics and metabolism in early drug discovery. Current Opinion in Chemical Biology 3:373-378. http://biomednet.com/elecref/1367593100300373. ISSN: 1367-5931.
[18] Kola I, Landis, J (2004) Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3:711-715. DOI: 10.1038/nrd1470.
[19] Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD (2002) Molecular properties that influence the oral bioavailability or drugs. J Med Chem 45 (12), 2615-2623. DOI: 10.1021/jm020017n.
[20] Van de Waterbeemd H, Smith DA, Beaumont K, Walker DK (2001) Property-based design:optimization of drug absorption and pharmacokinetics. J. Med. Chem., 44 (9), 1313-1333. DOI: 10.1021/jm000407e.
[21] Bodor N, Buchwald P (1997) Molecular size based approach to estimate partition properties for organic solutes. J. Phys Chem. B, 101(17), 3404-3412. DOI: 10.1021/jp9638503.
[22] Buchwald P, Bodor N (1998) Octanol-water partition:searching for predicting models. Curr. Med. Chem. 5: 353-380. ISSN: 0929-8673. http://cat.inist.fr/?aModele=afficheN&cpsidt=2422632
[23] Kubinyi H (1979). Nonlinear dependence of biological activity on hydrophobic character: the bilinear model. *Farmaco Sci* 34: 248–76. PMID 43264.
[24] Clark D E (1999) Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 1. Prediction of intestinal absorption. J. Pharm. Sci. 88(8), 807-814. DOI: 10.1021/js9804011.
[25] Raevsky OA, Schaper KJ (1998) Quantitative estimation of hydrogen bond contribution to permeability and absorption processes of some chemicals and drugs. Eur. J. Med. Chem. 33 (10), 799-807. DOI: 10.1016/S0223-5234(99)80031-2.
[26] Smith JD, Cappa CD, Wilson KR, Messer BM, Cohen RC, Saykally RJ (2004) Energetics of Hydrogen Bond Network Rearrangements in Liquid Water Science, 306: 29, 851-853. www.sciencemag.org/cgi/content/full/306/5697/851/DC1.
[27] Steimer JL, Vozeh S, Racine-Poon A (1994) The Population Approach: Rationale, Methods, and Applications in Clinical Pharmacology and Drug Development" (Chapter 15), in Welling PG, Balant LP, (eds.), Pharmacokinetics of Drugs (Handbook of Experimental Pharmacology), Berlin-Heidelberg: Springer-Verlag. Vol 110:404-451. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf
[28] Olson GL, Bolin DR, Bonner MP, Bos M, Cook CM, Fry DC, Graves BJ, Hatada M, Hill DE, (1993) Concepts and progress in the development of peptide mimetics. J. Med. Chem., 36 (21), 3039–3049. DOI: 10.1021/jm00073a001
[29] Maligres PE, Upadhyay V, Rossen K, Cianciosi SJ, Purick RM, Eng KK, Reamer RA, AsKin D, Volante RP, Reider PJ (1995) Diastereoselective syn-epoxidation of 2-alkyl-4-enamides to epoxyamides: Synthesis of the Merck HIV-1 protease inhibitor epoxide intermediate. Tetrahedron Lett. 36, 2195. DOI: 10.1016/0040-4039(95)00273-F.
[30] Hansch C, Fujita T, (1964) p-σ-π analysis. A method for the correlation of biological activity and chemical structure. J. Am. Chem. Soc. *86*: 1616-1626.
[31] Sahu VK, Khan AKR, Singh RK, Singh PP (2009) Drug-Receptor Interaction Based Quantitative Structure-Activity Relationship of Tetrahydroimidazodiazepinone. Int. J. Quantum Chem. 109: 1243-1254. DOI: 10.1002/qua.21942

Science Publications

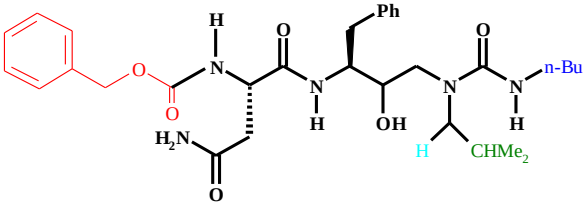
Universal Journal of Pharmacy and Pharmacology, 2022, 1, 403
www.scipublications.org/journal/index.php/ujpp
DOI: 10.31586/ujpp.2022.403

Appendix

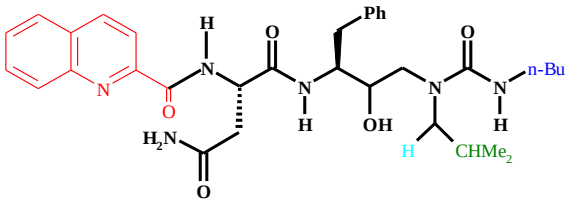
Scheme 1. Structure of peptidic HIV-1 protease inhibitors



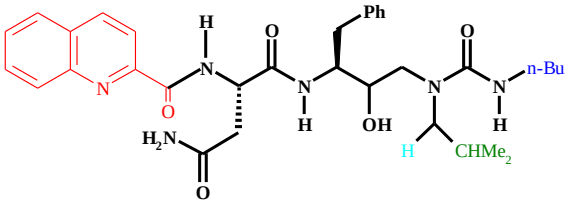
1



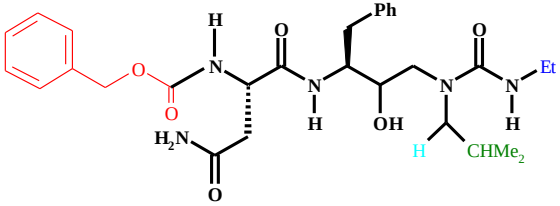
2



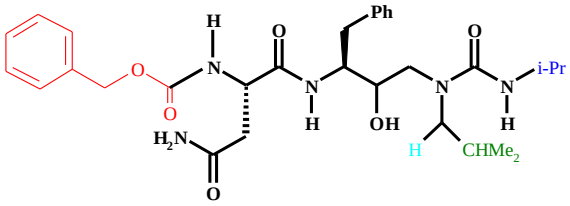
3



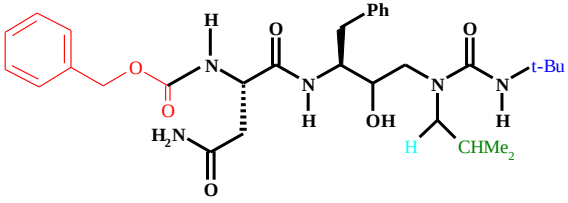
4



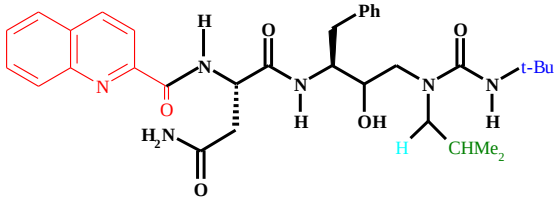
5



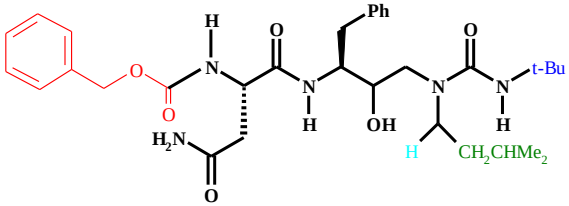
6



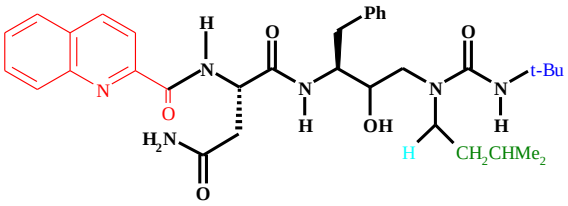
7



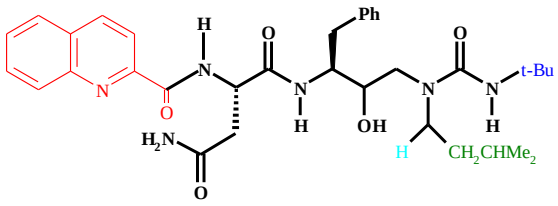
8



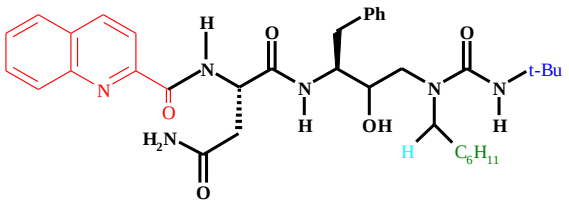
9



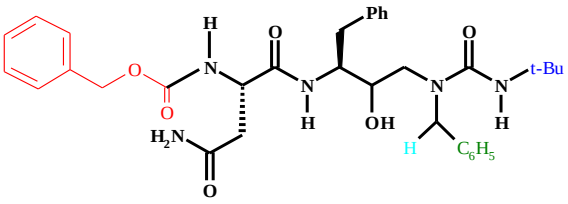
10



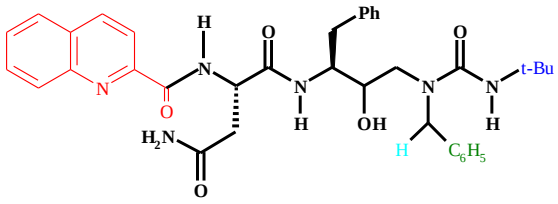
11



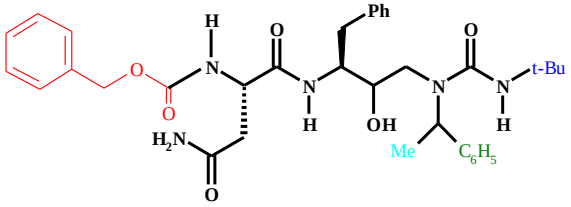
12



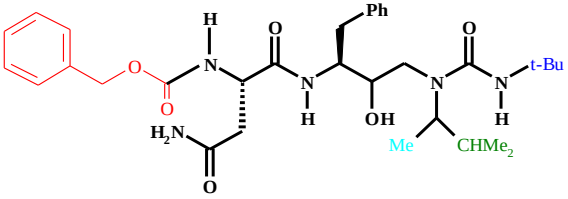
13



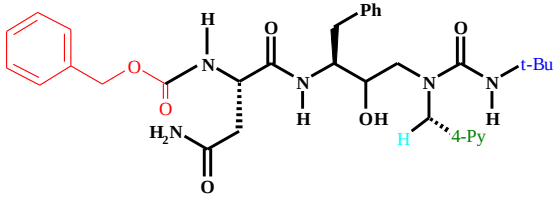
14



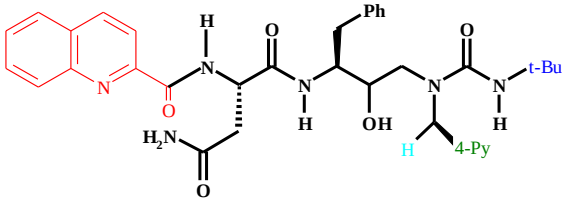
15



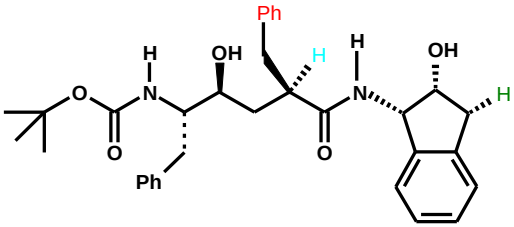
16



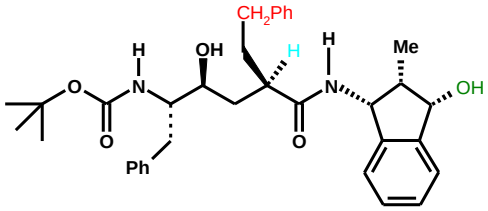
17



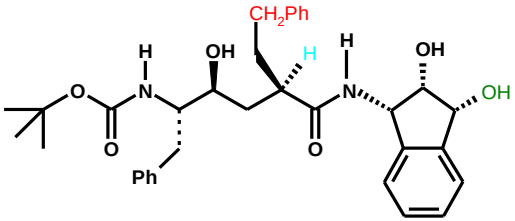
18



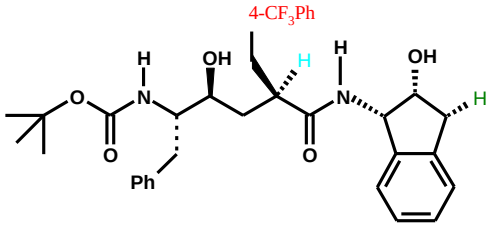
19



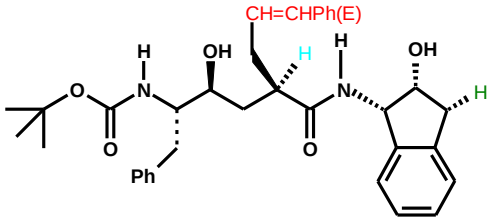
20



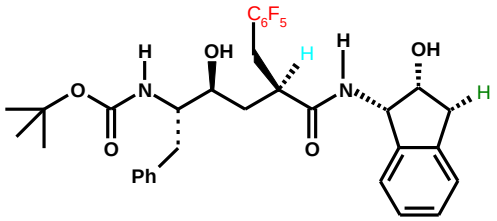
21



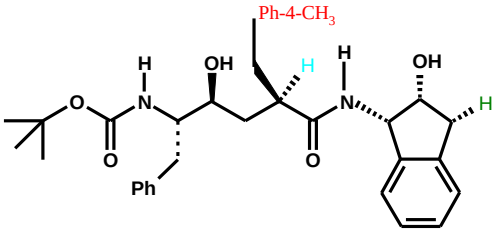
22



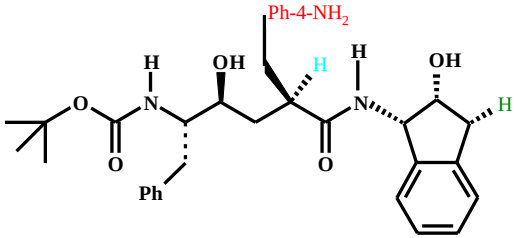
23



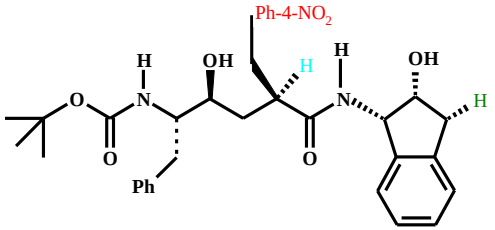
24



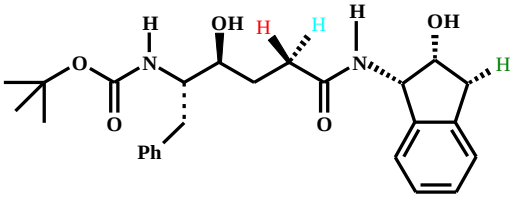
25



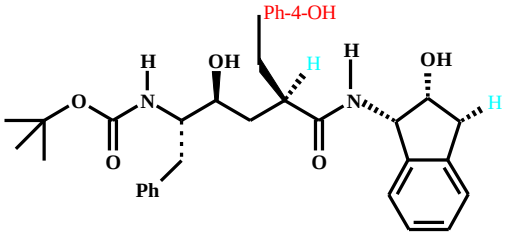
26



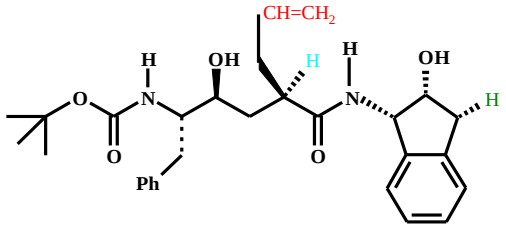
27



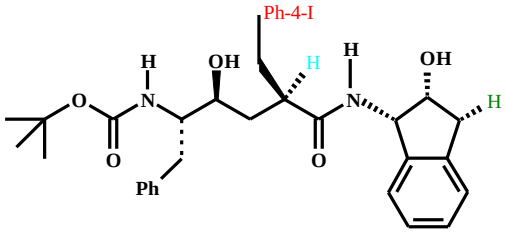
28



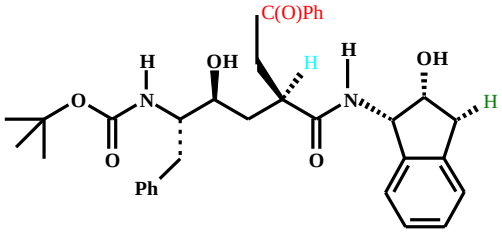
29



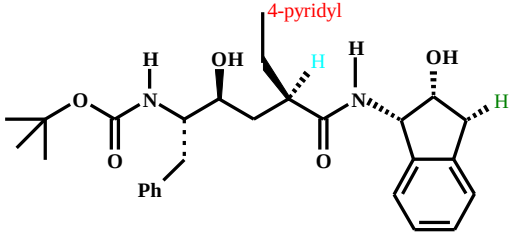
30



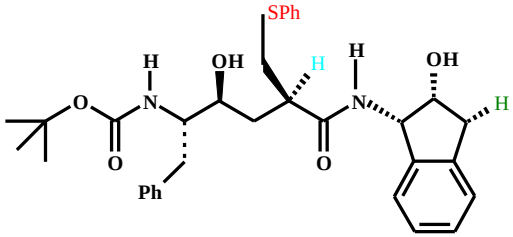
31



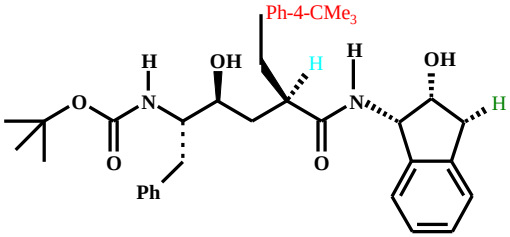
32



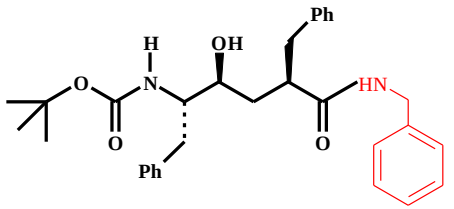
33



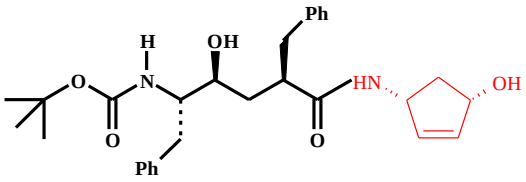
34



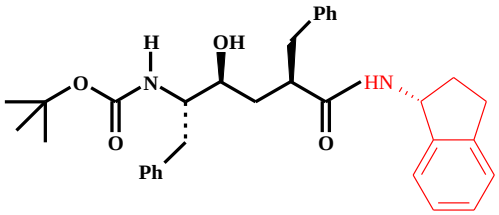
35



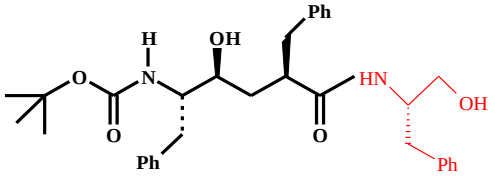
36



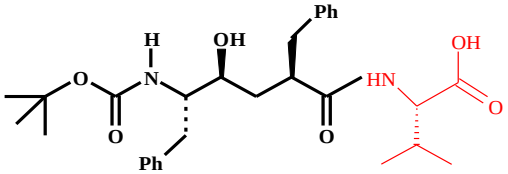
37



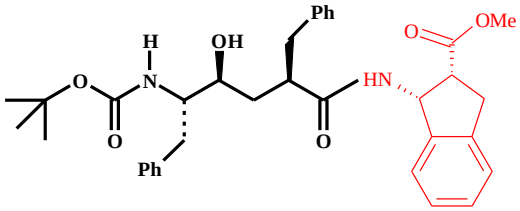
38



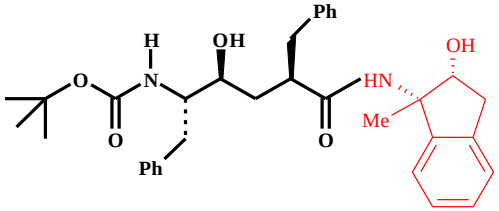
39



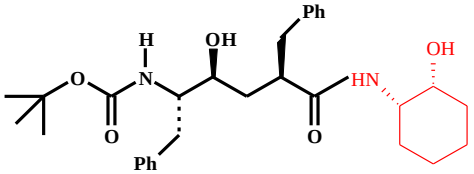
40



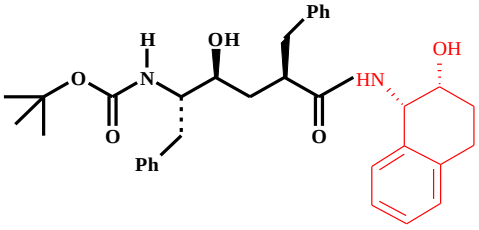
41



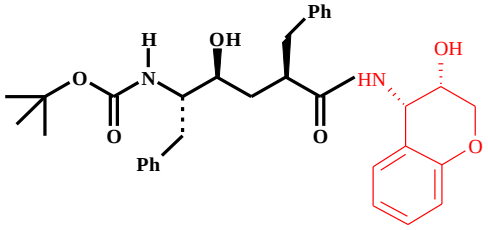
42



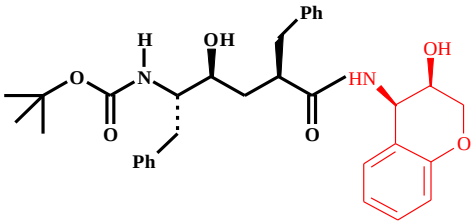
43



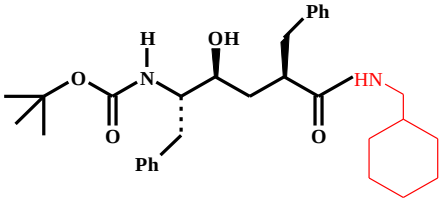
44



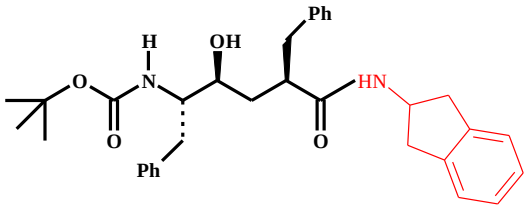
45



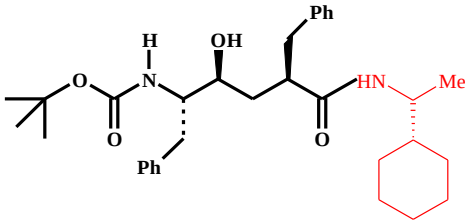
46



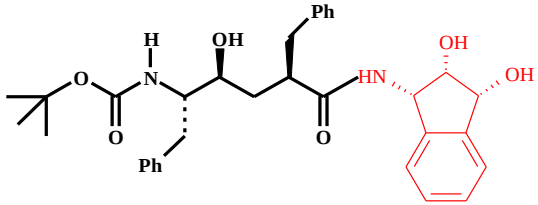
47



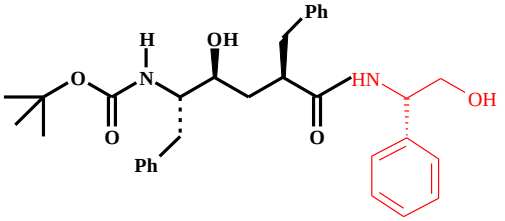
48



49

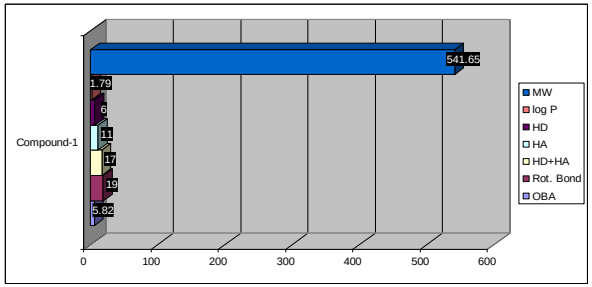


50

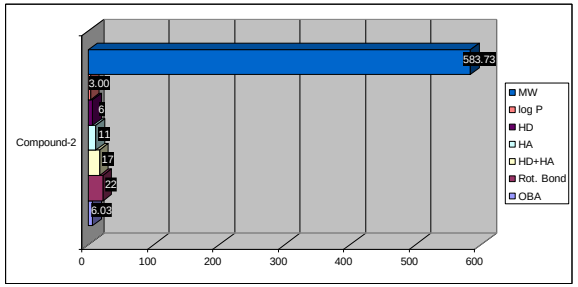


51

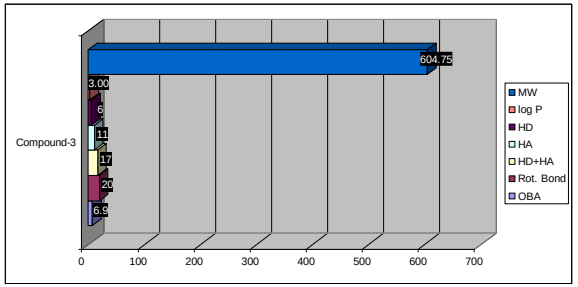
Scheme 2. Graphical representation of rule of five of peptidic HIV-1 protease inhibitors



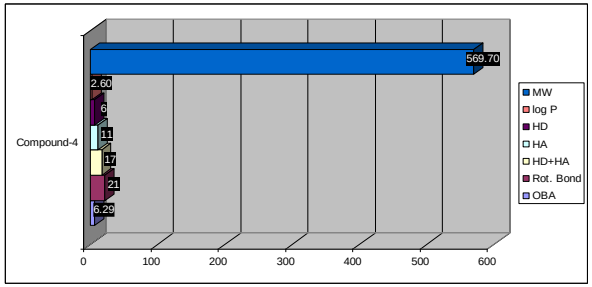
1



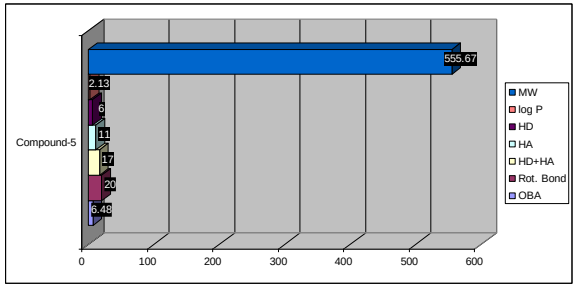
2



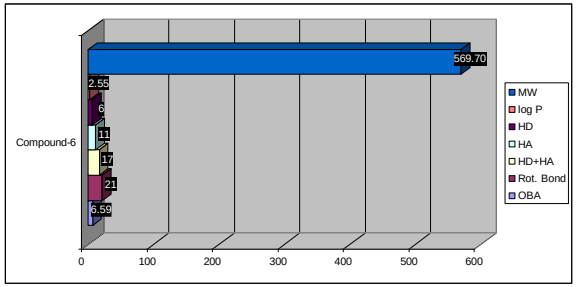
3



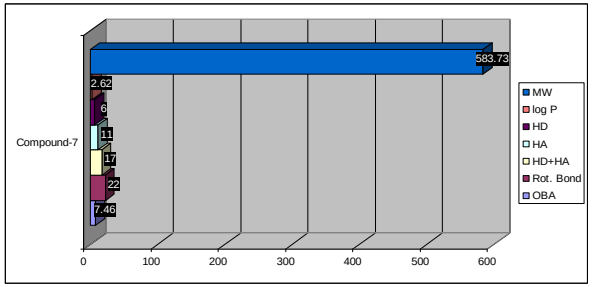
4



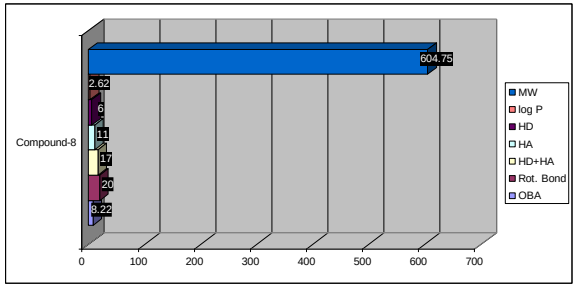
5



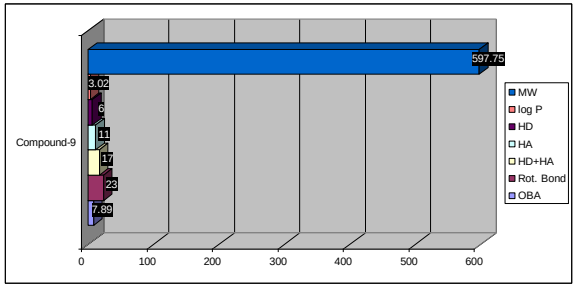
6



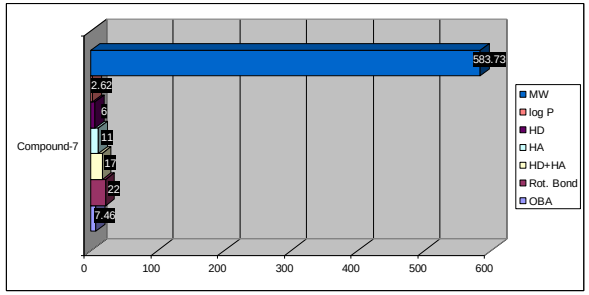
7



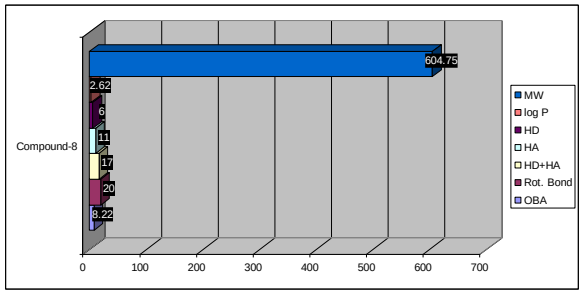
8



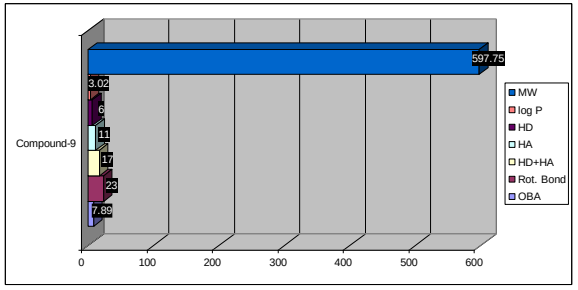
9



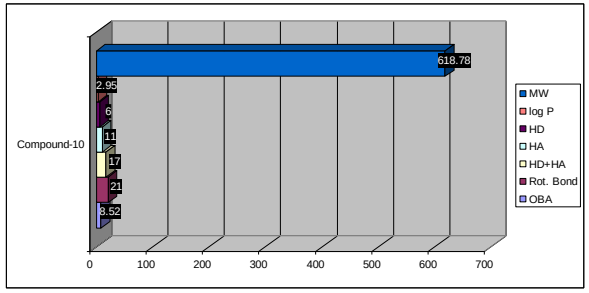
10



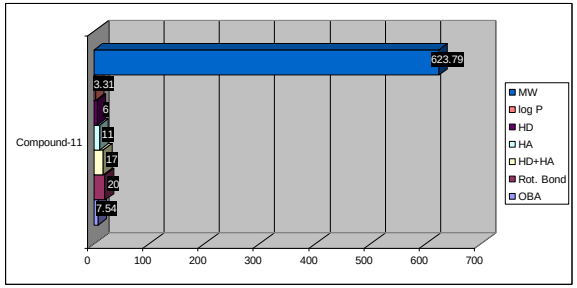
11



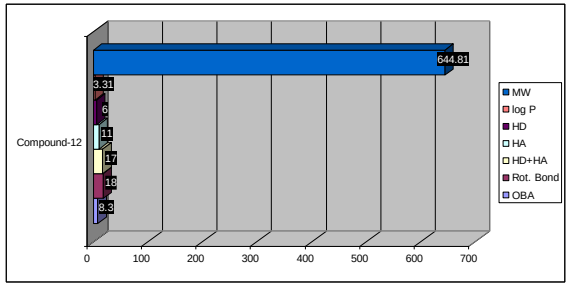
12



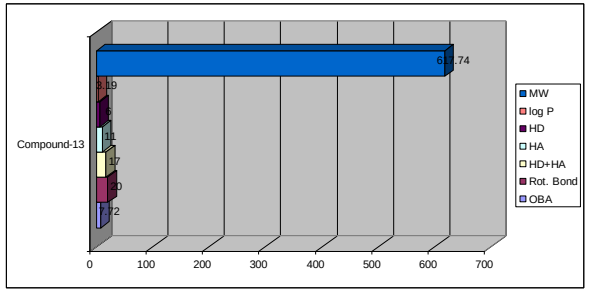
13



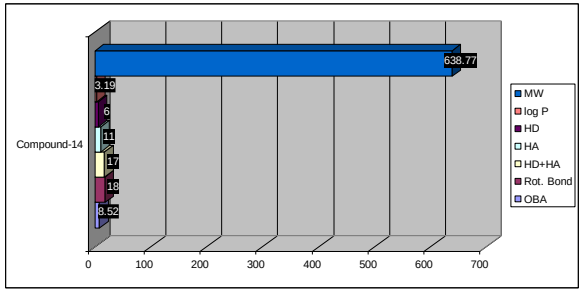
14



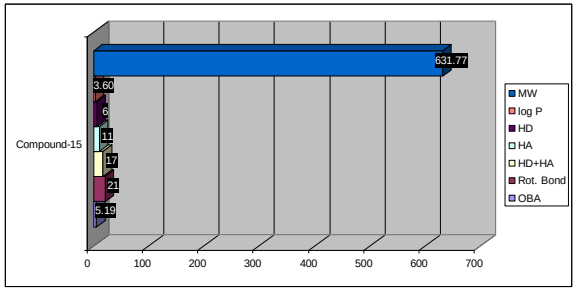
15



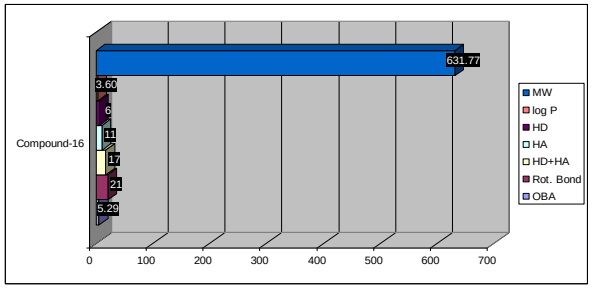
16



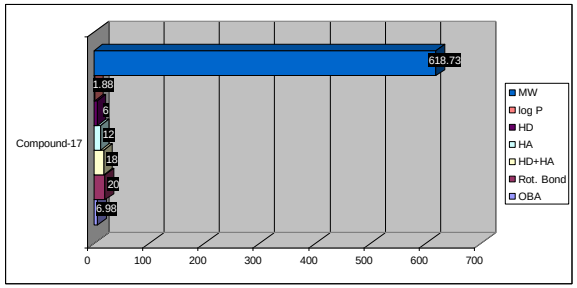
17



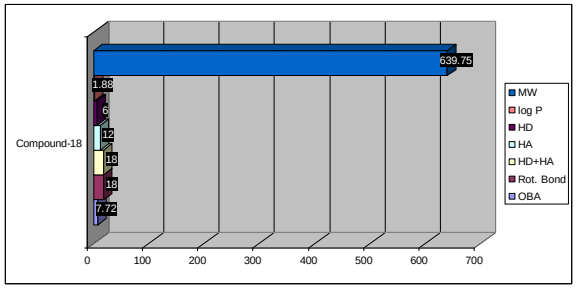
18



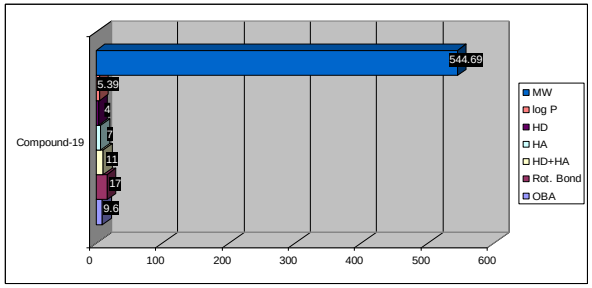
19



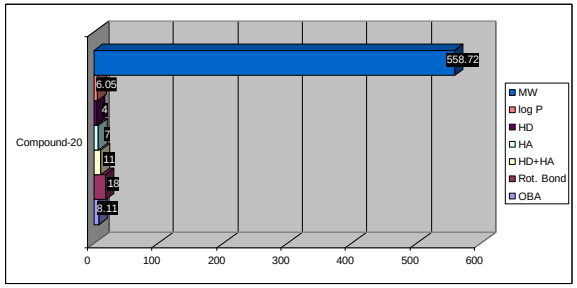
20



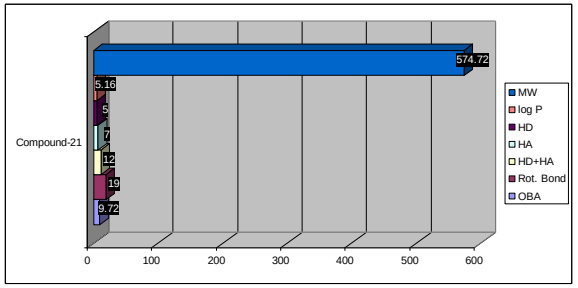
21



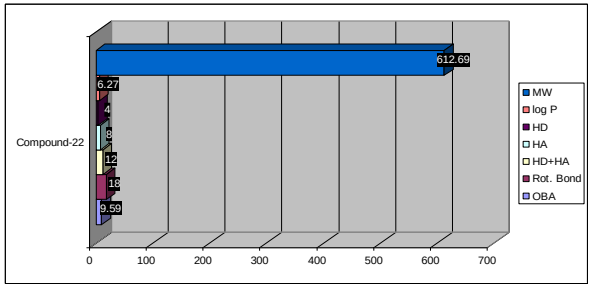
22



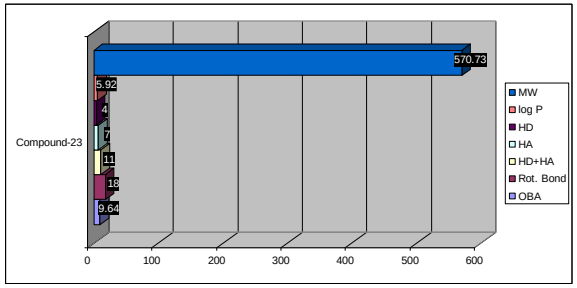
23



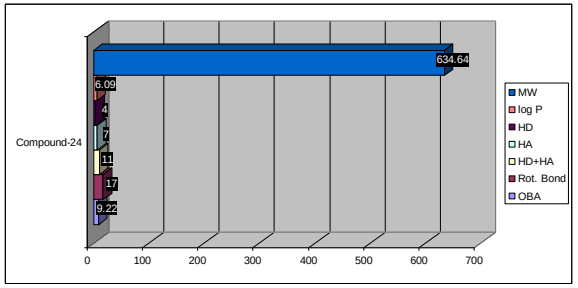
24



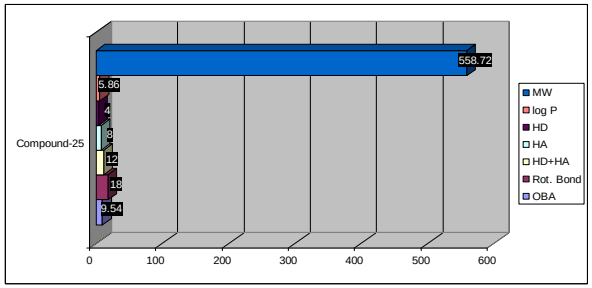
25



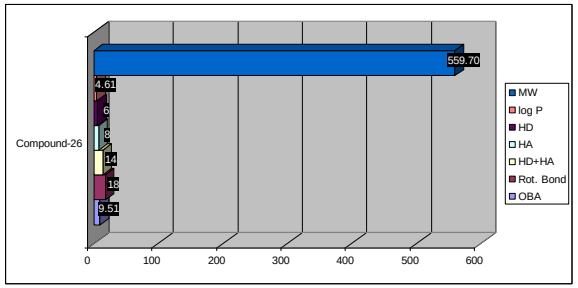
26



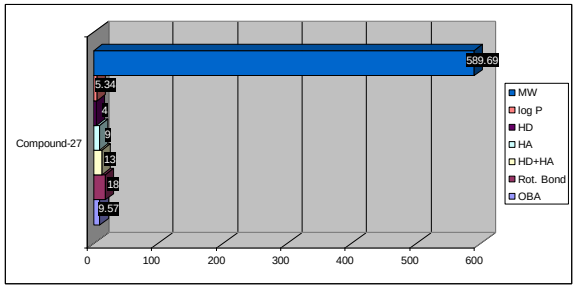
27



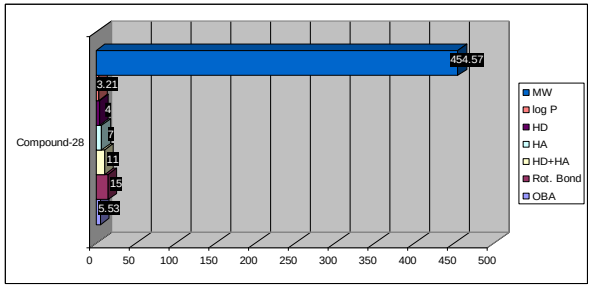
28



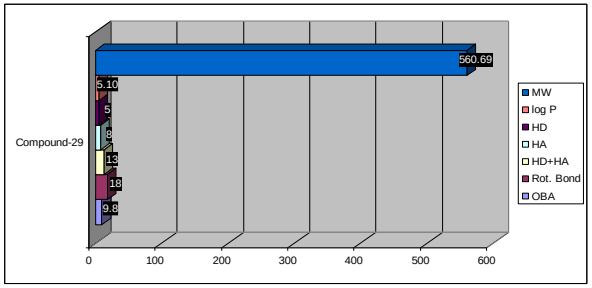
29



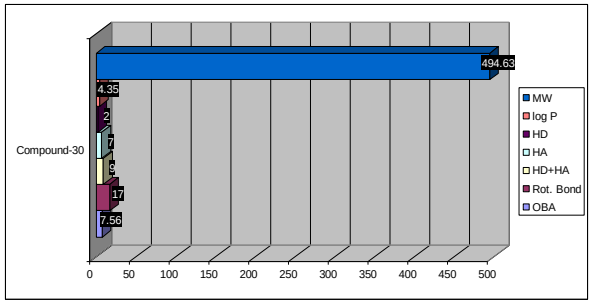
30



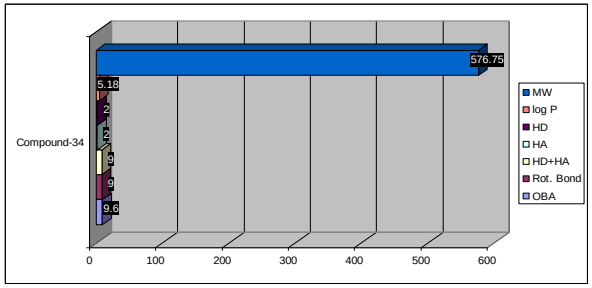
31



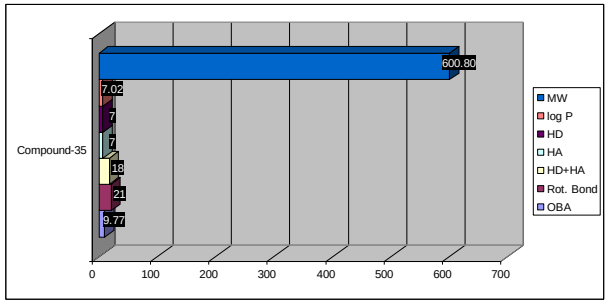
32



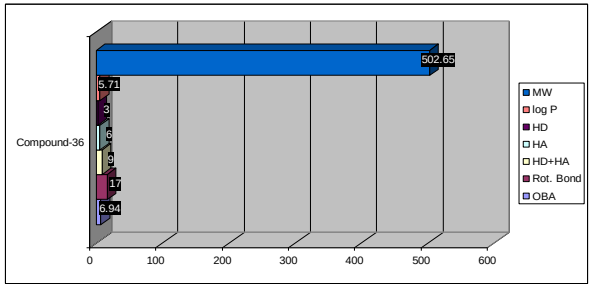
33



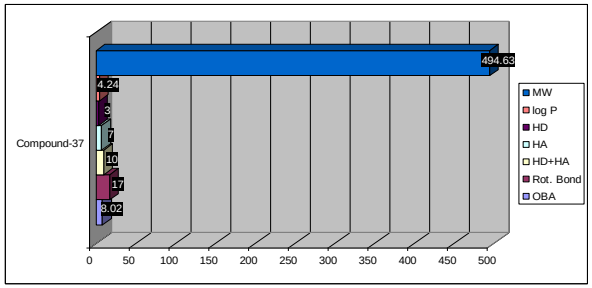
34



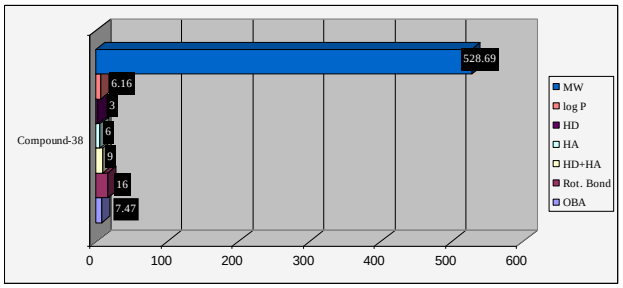
35



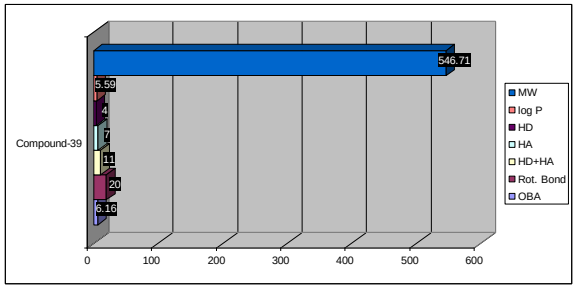
36



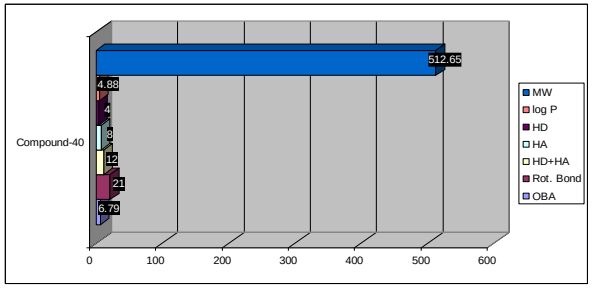
37



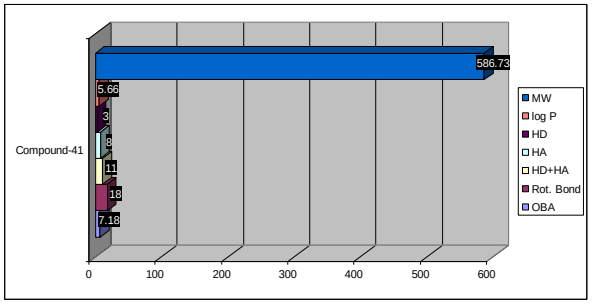
38



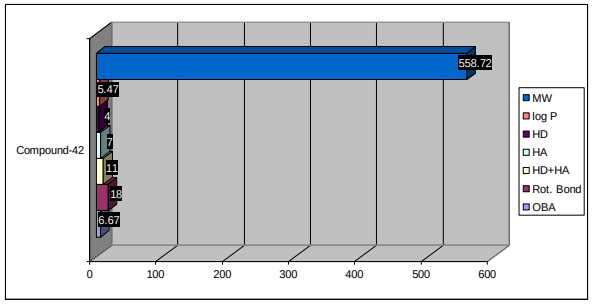
39



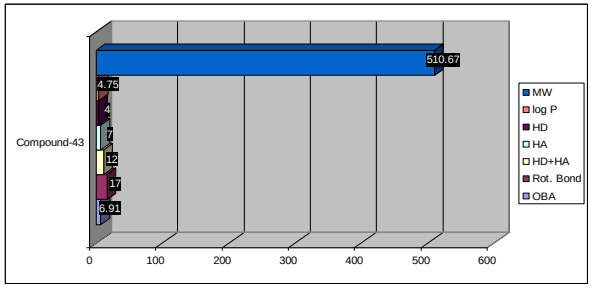
40



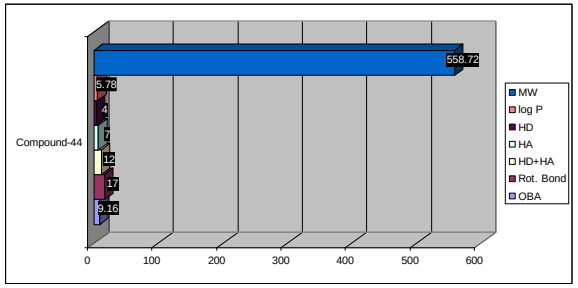
41



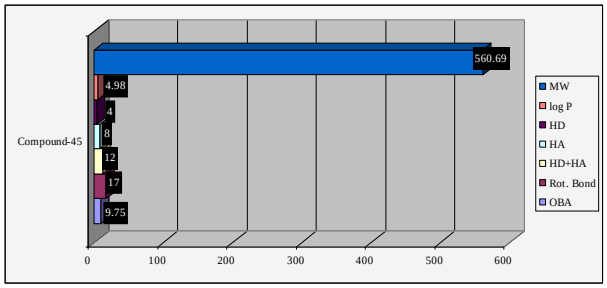
42



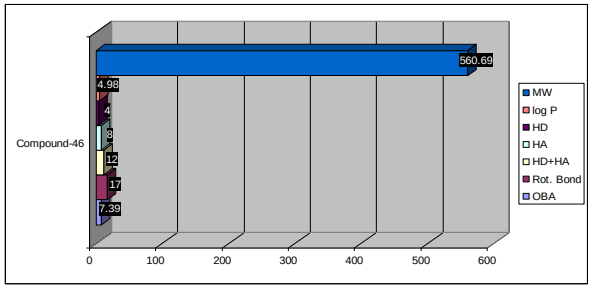
43



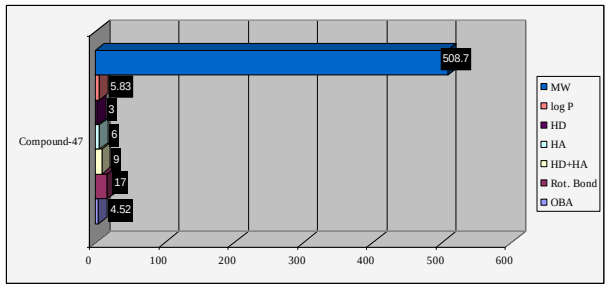
44



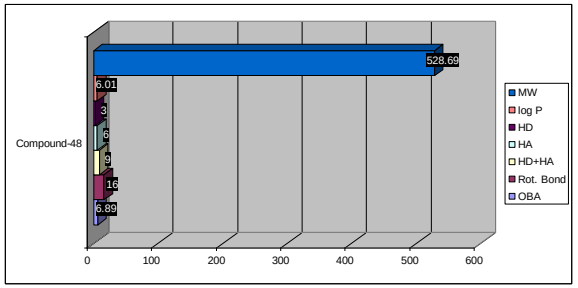
45



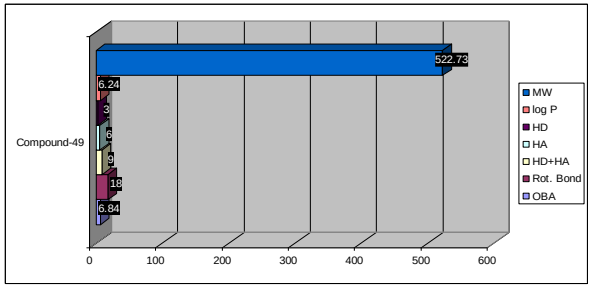
46



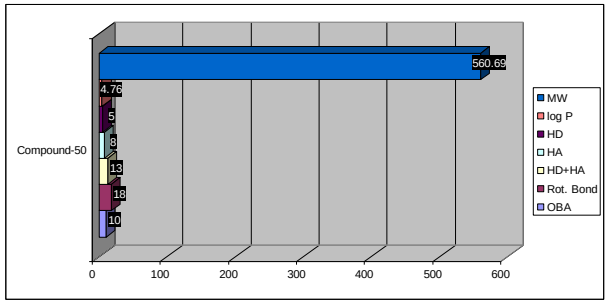
47



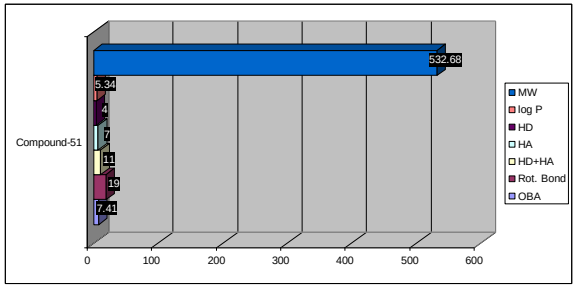
48



49



50



51