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QSAR STUDIES ON THE HEPT DERIVATIVES OF HIV-1 REVERSE TRANSCRIPTASE

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ABSTRACT

QSAR analysis on a set of HEPT derivatives for antiviral activity was performed by using multiple regression procedure. The activity contribution of these compounds were determined from regression equation and the validation procedure to analyze the predictive ability of QSAR model were described. High agreement between experimental and predicted inhibitory values was obtained. The results of this study indicate that the parameter has a significant effect on antiviral activity of this class of compounds, thus simplifying design of new biologically active molecules.

KEYWORDS: Topological descriptors, MLR, QSAR/QSPR.

INTRODUCTION

Reverse Transcriptase (RT) is one of the key enzymes, which plays an essential role in the replication cycle of the human immunodeficiency virus type 1 (HIV-1). The HIV-1 RT is responsible for the conversion of the single-stranded RNA retroviral genome into the double-stranded proviral DNA, which is then integrated into the host cell chromosome. [1,2] The HIV-1 RT enzyme shows both RNA- and DNA-dependent polymerase activities. Among several targets identified for the therapeutic intervention of the HIV-1 life cycle, the lack of RT activity in the eukaryotic cells has made RT as one of the most attractive targets for the development of anti-HIV-1 agents. [3,4]

The NNRTI inhibit the enzyme by an allosteric interaction with the adjacent site to the NRTI binding site. [19–27] It has been shown that the NNRTIs can suppress the virus replication in cell cultures for at least 3 months, while under the same condition; NRTIs cannot control the virus replication even after a few days in the continued presence of the compound. [28–30] Thus, NNRTIs have been considered as the prime inhibitors of HIV-1 RT. The NNRTIs are highly specific because of their hydrophobic binding site located at _10 _ away from the polymerase binding site. However, the high specific binding with the allosteric site is limited by the mutations at the NNRTI binding site, and it causes loss of antiviral activity of all NNRTI drugs. [31,32] Until now, there are more than 15 structurally diverse set of NNRTIs have been identified for the inhibition of mutational resistance developed by HIV-1 RT.

The present scenario calls for further investigation into the identification of structurally more diverse set of HIV-1 RT inhibitors to circumvent the mutational resistance. The HEPT was the first NNRTI synthesized in 1989. In the development of new inhibitors, the HEPT has been considered as the lead compound. [3,33] Several Quantitative Structure Activity Relationship (QSAR) studies have been carried out on the NNRTI derivatives. [34–42] Chiu and coworkers have reported neural network-based QSAR studies of various HEPT derivatives using Hansch substituent constants as possible descriptors. [43] A detailed report on the anti-HIV activity of HEPT, TIBO, TSAO, nevirapine, pyridinone, and a-PAP derivatives [35] has been reviewed by Hansch and coworkers.

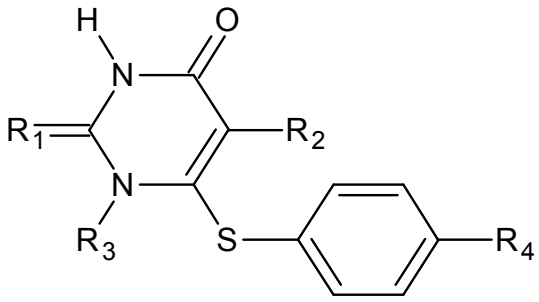

Fig 1: General structure of HEPT Derivatives non-peptide HIV-1 Reverse Transcriptase.

MATERIALS AND METHODS

Data sets and molecular preparation

The training and test sets consist of 36 and eight molecules, respectively, which are shown to be a potent inhibitor against HIV-1 activity. [45,46] The molecules of the test set were chosen randomly to represent wide activity range and the structural diversity. The experimental

activity data shown in Table 1 refers to the ability of the compound to protect MT-4 cells against the cytopathic effect of the virus. The parameter EC50 stands for the minimum concentration of the compounds required to achieve 50% protection of the cells. For QSAR analysis, EC50 values were transformed into log (1/EC50) values and then used as response variables. This data set is extensively used in the previous QSAR study. [37]

It provides a further opportunity for QSAR study to quantify the relationship between three-dimensional molecular structure and biological activity. The molecular structures of the training and test set compounds were constructed using the chemsketch12 and e-dragon software developed by (Milano Chemometrics and QSAR Research Group, Milano, Italy) software.

Table 1: General Structure of the compounds with their substitutions

C No.	R1	R2	R3	R4	pIC_{50}
1	0	Me	$CH_2OCH_2CH_2OH$	3-CF_3	4.35
2	0	Me	$CH_2OCH_2CH_2OH$	3-NO_2	4.47
3	0	Me	$CH_2OCH_2CH_2OH$	2-OMe	4.72
4	0	Me	$CH_2OCH_2CH_2OH$	3-Cl	4.89
5	0	Me	$CH_2OCH_2CH_2OH$	3-CN	5
6	S	Pr	$CH_2OCH_2CH_2OH$	H	5
7	0	Me	$CH_2OCH_2CH_2OH$	3-COOMe	5.1
8	0	Me	$CH_2OCH_2CH_2OH$	3-COMe	5.14
9	0	Me	$CH_2OCH_2CH_2OH$	H	5.15
10	0	Me	$CH_2OCH_2CH_2OH$	3-Br	5.24
11	0	I	$CH_2OCH_2CH_2OH$	H	5.44
12	0	Pr	$CH_2OCH_2CH_2OH$	H	5.47
13	0	Me	$CH_2OCH_2CH_2OH$	3-F	5.48
14	0	Me	$CH_2OCH_2CH_2OH$	3-Et	5.57
15	0	Me	$CH_2OCH_2CH_2OH$	3-Me	5.59
16	0	Me	CH_2OMe	H	5.68
17	0	Me	$CH_2OCH_2CH_2Cl$	H	5.82
18	0	Me	$CH_2OCH_2CH_2OH$	3,5-Cl	5.89
19	0	Me	$CH_2OCH_2CH_2F$	H	5.96
20	0	Me	CH_2OCH_2Me	H	6.48
21	0	Me	$CH_2OCH_2CH_2OH$	3,5-Me	6.59
22	S	Me	$CH_2OCH_2CH_2OH$	3,5-Me	6.66
23	0	Et	$CH_2OCH_2CH_2OH$	H	6.92
24	0	Et	$CH_2OCH_2CH_2OH$	H	6.96
25	0	i-Pr	$CH_2OCH_2CH_2OH$	H	7.2
26	S	i-Pr	$CH_2OCH_2CH_2OH$	H	7.23
27	S	Et	$CH_2OCH_2CH_2OH$	3,5-Cl	7.37
28	0	Et	CH_2OCH_2Me	H	7.72
29	S	i-Pr	CH_2OCH_2Me	H	7.85

30	0	Et	$CH_2OCH_2CH_2OH$	3,5-Me	7.89
31	S	Et	CH_2OCH_2Me	3,5-Cl	7.89
32	0	i-Pr	CH_2OCH_2Me	H	7.92
33	0	Et	CH_2OCH_2Me	3,5-Cl	8.13
34	0	Et	CH_2OCH_2Me	3,5-Me	8.27
35	S	i-Pr	$CH_2OCH_2CH_2OH$	3,5-Me	8.3
36	0	i-Pr	$CH_2OCH_2CH_2OH$	3,5-Me	8.57
37	0	Me	$CH_2OCH_2CH_2OH$	4-Me	3.66
38	0	Me	$CH_2OCH_2CH_2OH$	3-OH	4.09
39	0	Me	$CH_2OCH_2CH_2OH$	3-I	5
40	S	Me	$CH_2OCH_2CH_2OH$	H	6.01
41	S	Et	CH_2OCH_2Me	H	7.59
42	0	Et	$CH_2OCH_2CH_2OH$	3,5-Cl	7.85
43	S	Et	$CH_2OCH_2CH_2OH$	3,5-Me	8.11
44	S	Et	CH_2OCH_2Me	3,5-Me	8.36

Descriptor Generation

All structures were generated with the chemsketch12 ACD labs program and optimized by the AM1 semi-empirical method of the software. Since the calculated values of the electronic features of the molecules will be influenced by the conformation used, in the current research we made attempt to use the most stable conformations. To avoid the local stable conformations of the compounds, geometry optimization was run many times with different starting points for each molecule, and conformation with the lowest energy was considered for calculation of the electronic properties. Constitutional descriptors and topological indices were calculated utilizing Dragon software created by the Milano QSAR and Chemometrics Research Group (www.disat.unimib.it/chm/). These descriptors are calculated using two-dimensional representation of the molecules and therefore geometry optimization is not essential for calculating these types of descriptors. In addition, Dragon calculates a large number of descriptors from the optimized three dimensional structure of the molecules.

Table 2: Calculated physicochemical and topological descriptors

pIC50	MR	MV	MSD	MAXDN	X0
4.35	85.25	252.6	5.715	6.003	18.613
4.47	86.29	232.7	5.585	2.813	17.69
4.72	86.62	243.3	5.251	2.759	16.82
4.89	85.09	232.3	5.196	2.714	16.113
5	84.83	230.8	5.416	2.742	16.82
5	96.52	262	5.219	2.364	16.656
5.1	91.37	256.4	5.808	2.798	18.397
5.14	89.63	250.3	5.585	2.783	17.69
5.15	80.26	221.4	5.036	2.683	15.242
5.24	87.98	234.2	5.196	2.693	16.113

5.44	88.56	225	5.036	2.568	15.242
5.47	89.52	253.9	5.219	2.674	16.656
5.48	80.37	226	5.196	2.775	16.113
5.57	89.51	253.4	5.416	2.73	16.82
5.59	84.88	237.2	5.196	2.728	16.113
5.68	74.09	207.8	4.473	2.651	13.828
5.82	83.56	235.4	5.036	2.629	15.242
5.89	89.91	243.2	5.321	2.735	16.983
5.96	78.84	229.1	5.036	2.703	15.242
6.48	78.72	224	4.728	2.643	14.535
6.59	89.51	253	5.321	2.763	16.983
6.66	96.5	261.1	5.321	2.537	16.983
6.92	84.89	237.7	5.091	2.675	15.949
6.96	91.89	245.8	5.091	2.387	15.949
7.2	89.5	254.5	5.128	2.735	16.82
7.23	96.49	262.6	5.128	2.503	16.82
7.37	101.54	267.6	5.368	2.44	17.69
7.72	83.25	240.3	4.795	2.636	15.242
7.85	94.96	265.3	4.841	2.476	16.113
7.89	94.14	269.2	5.368	2.756	17.69
7.89	100.01	270.2	5.088	2.413	16.983
7.92	87.96	257.1	4.841	2.695	16.113
8.13	93.01	262.1	5.088	2.688	16.983
8.27	92.6	271.8	5.088	2.716	16.983
8.3	99.06	258.7	5.085	2.402	17.43
8.57	98.74	286	5.399	2.815	18.56
3.66	84.88	237.2	5.294	2.721	16.113
4.09	81.79	218.4	5.196	2.759	16.113
5	93.18	240.8	5.196	2.683	16.113
6.01	87.26	229.6	5.036	2.457	15.242
7.59	90.35	248.4	4.795	2.36	15.242
7.85	94.55	259.4	5.368	2.728	17.69
8.11	101.13	277.3	5.368	2.467	17.69
8.36	99.6	280	5.088	2.441	16.983

Data Preprocessing

In the case of each antiviral activity, the calculated descriptors were collected in a data matrix (**D**) with dimension of ($n \times m$), where n and m are being the number of molecules in each data set and the number of calculated descriptors for each molecule, respectively. Firstly, the descriptors were checked for constant or near constant values and those detected were removed from the original data matrix. Then, the correlation of descriptors with each others and with the activity data was determined. Among the collinear descriptors detected ($r > 0.9$), one of them that had the highest correlation with activity was retained and the rest were ommited.

Model Development and Validation

QSAR models were obtained by multiple linear regression (MLR) analysis. The stepwise selection of variables, a combination of forward selection and backward elimination procedure, was used to select the most relevant subset of descriptors. Regression analyses were performed by NCSS software (NCSS Inc., Version 11.5). In the case of each regression problem, NCSS produces many models and ranked them based on standard error of calibration (Se) and coefficient of multiple determinations (R2), where some models have large number of input variables and thus they are over-fitted.

Table 3: Correlation matrix

	pIC50	MR	MV	MSD	MAXDN	X0
pIC_{50}	1.0000					
MR	0.6183	1.0000				
MV	0.6993	0.8750	1.0000			
MSD	-0.3472	0.1703	0.1929	1.0000		
MAXDN	-0.3090	-0.2283	-0.0174	0.5142	1.0000	
X0	0.2341	0.6121	0.6958	0.7694	0.4070	1.0000

To hinder obtaining over-fitted models, the generated multilinear QSAR models by NCSS were validated by cross-validation for prediction ability and generalization. A balance between the high cross-validation correlation coefficient (R_2^{CV}) and low number of descriptors were used as the criterion for model selection. The overall prediction abilities of the final models were accessed by using prediction set containing about 25% of the original molecules. To do so, the data sets of each antiviral activity were classified to calibration and prediction sets, randomly. The model coefficients were calculated using calibration data and then used to calculate the antiviral activity of the molecules in the prediction set. The data splitting was run seven times and the root mean square errors of predictions were averaged.

RESULTS AND DISCUSSION

To investigate the effects of molecular structure on the antiviral activity of the studied natural compounds, a large number of molecular descriptors belonging to wide variety of structural features were considered. At the first, separate QSAR models were obtained using the pools of different type of molecular descriptors. This helped us to identify the molecular descriptors of each group that represented higher impact oh the antiviral activity of interest. Then, the selected descriptors of different types were used to develop a final QSAR model for each data set.

Table 4: Developed QSAR models using training set of 36 molecules with Statistical and Cross Validated statistical descriptors.

Eq. No.	QSAR/QSPR Models	N	R^2	R^2adj	MSE	PRESS	R^2cv	CV	F
1	pIC_{50} = -7.9057+ 5.7217E-02MV	36	0.48	0.47	1.01	37.59	0.44	0.16	32.55
2	pIC_{50} = 20.9596-8.6228MSD+ 1.8183X0	36	0.74	072	0.54	20.87	0.69	0.11	46.22
3	pIC_{50} = 14.1873-6.3286MSD + 3.3525E-02*MV+ 1.0049X0	36	0.78	0.75	0.47	18.76	0.72	0.10	36.79

Table 5: Developed QSAR models using test set of 08 molecules with Statistical and Cross Validated statistical descriptors.

Eq. No.	QSAR/QSPR Models	N	R^2	R^2adj	MSE	PRESS	R^2cv	CV	F
1	pIC_{50} = 24.6499-6.9062MAXDN	08	0.50	0.42	1.19	10.84	0.25	0.17	05.99
2	pIC_{50} = 5.2981-2.9400MSD + 6.6486E-02MV	08	0.96	0.94	0.12	21.73	0.88	0.05	55.65

The resulted QSAR models derived from the pools of different types of molecular descriptors is represented in Table 2 for the anti-HIV agents. It is clearly observed that no accurate model has been obtained from none of the descriptor types. However, significant QSAR models have been obtained from the pool of some descriptor represented the most significant QSAR model. These descriptors are comprehensively described. The cross-validated correlation coefficients (R2 CV) of the QSAR models derived from these types of descriptors are higher than 0.70, which means that these models could explain more than 88% of the variances in the anti-HIV activity of the studied natural compounds.

Table 6: Developed QSAR models using total set of 44 molecules with Statistical and Cross Validated statistical descriptors.

Eq. No.	QSAR/QSPR Models	N	R^2	R^2adj	MSE	PRESS	R^2cv	CV	F
1	pIC_{50} = -6.4766+ 5.1678E-02MV	44	0.46	0.44	1.06	48.20	0.41	0.16	35.17
2	pIC_{50} = 6.5005-3.1628MSD+ 6.5457E-02MV	44	0.76	0.75	0.47	21.29	0.74	0.10	66.51
3	pIC_{50} = 10.7146-5.3941MSD + 4.2386E-02MV +0.7905X0	44	0.79	0.77	0.42	20.35	0.75	0.10	50.99
4	pIC_{50} = 11.3034-0.3418MAXDN-5.5501MSD+ 3.5670E-02MV + 0.9606X0	44	0.81	0.78	0.40	21.37	0.73	0.10	40.27

After deletion of three serious outliers compound no.03,06 and 36.									
5.	pIC_{50} = 9.1978-0.3859MAXDN-4.5679MSD+ 4.3903E-02MV + 0.6707X0	41	0.88	0.87	0.22	9.80	0.85	0.07	67.54

To obtain QSAR model containing different structural features of the studied molecules, the selected descriptors appeared in Table 3 were collected and QSAR models were generated from the pool of these descriptors. Among the different QSAR models proposed by SPSS software, that model represented the highest cross-validated correlation coefficient with lower number of input descriptors is represented in Table 4. In this table, the selected descriptors along with their regression coefficient and the corresponding

Table 7: The actual and predicted inhibitory anticancer activity

Compd. No.	pIC_{50}		Residual
	Obs.	Predicted	
1	4.35	4.351	-0.001
2	4.47	4.683	-0.213
3	4.89	5.423	-0.533
4	5	4.815	0.185
5	5.1	5.185	-0.085
6	5.14	5.467	-0.327
7	5.15	5.103	0.047
8	5.24	5.514	-0.274
9	5.44	5.305	0.135
10	5.47	6.646	-1.176
11	5.48	5.123	0.357
12	5.57	5.812	-0.242
13	5.59	5.632	-0.042
14	5.68	6.141	-0.461
15	5.82	5.738	0.082
16	5.89	5.906	-0.016
17	5.96	5.433	0.527
18	6.48	6.165	0.315
19	6.59	6.325	0.265
20	6.66	6.768	-0.108
21	6.92	6.044	0.876
22	6.96	6.511	0.449
23	7.2	7.174	0.026
24	7.23	7.619	-0.389
25	7.37	7.35	0.02
26	7.72	7.052	0.668
27	7.85	8.585	-0.735
28	7.89	7.299	0.591
29	7.89	8.28	-0.39
30	7.92	8.14	-0.22

31	8.13	7.818	0.312
32	8.27	8.233	0.037
33	8.3	8.093	0.207
34	8.57	8.455	0.115
35	4.09	4.795	-0.705
36	5	5.808	-0.808
37	6.01	5.55	0.46
38	7.59	7.514	0.076
39	7.85	6.879	0.971
40	8.11	7.766	0.344
41	8.36	8.699	-0.339

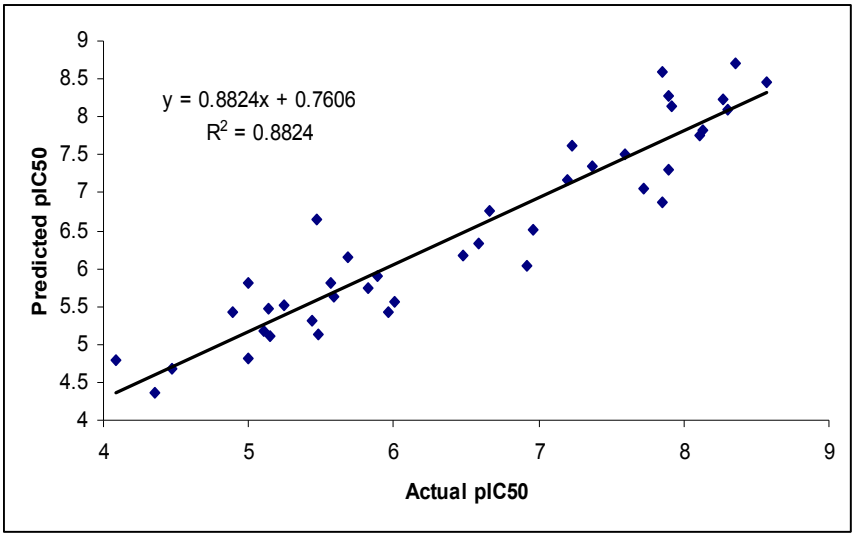

Fig 1: Graph plotted between actual pIC_{50} and predicted pIC_{50} inhibitory anticancer activity

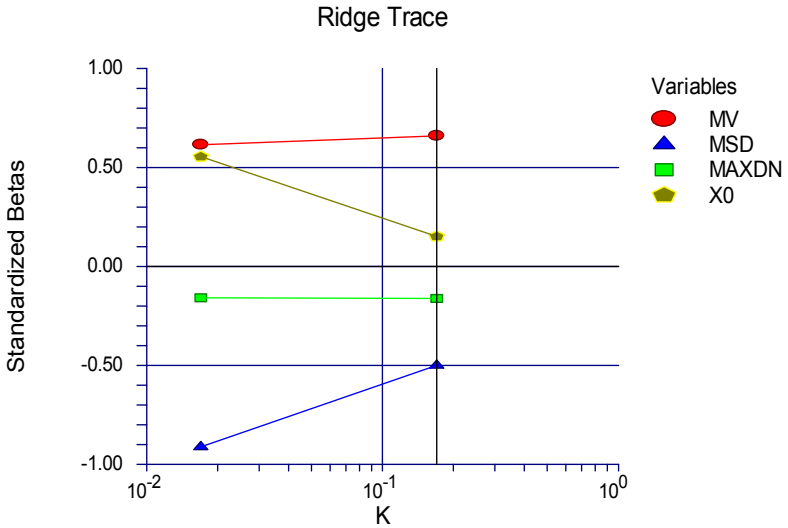

Fig 2: Graph plotted between k and standardized beats

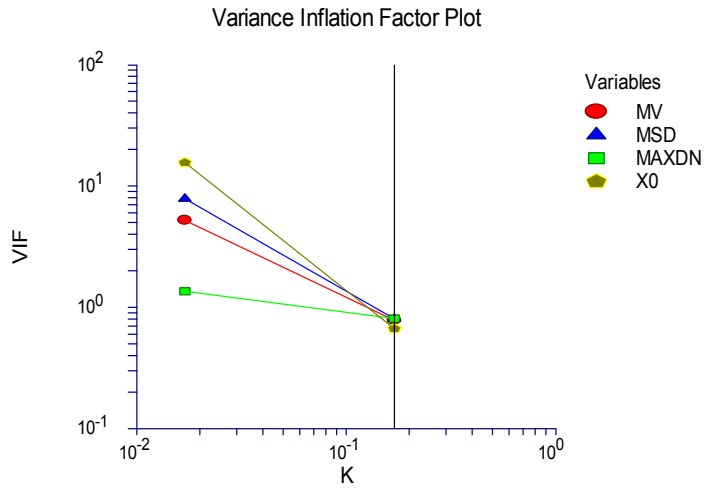

Fig 3: Graph plotted between k and VIF

The overall prediction ability of the resulted model was established by using prediction set samples. To do so, 36 molecules, out of 44 molecules, were randomly selected as prediction set and the rest were chosen as calibration samples. Model coefficients were calculated using calibration samples and then they used to predict the activity of the prediction samples. To investigate the effect data splitting on the model performances, data splitting into calibration and prediction sets was repeated seven times. The resulted correlation coefficients of the prediction sets are shown in Fig. 2A. Obviously, the resulted correlation coefficients are higher than 0.88, which shows the ability of the resulted QSAR model to predict 88% of the anti-HIV1 activity data.

REFERENCES

1. Fauci S. (1998) The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. Science, 1998; 239:617–622.
2. De Clercq E. (1995) Toward improved anti-HIV chemotherapy: therapeutic strategies for intervention with HIV infections. J Med Chem, 1995; 38:2491–2517.
3. Moore J.P., Stevenson M. (2000) New targets for inhibitors of HIV-1 replication. Nat Rev Mol Cell Biol, 2000; 1: 40–49.
4. Castro H.C., Loureiro N.I., Pujol-Luz M., Souza A.M., Albuquerque M.G., Santos D.O., Cabral L.M., Frugulhetti I.C., Rodrigues C.R. (2006) HIV-1 reverse transcriptase: a therapeutical target in the spotlight. Curr Med Chem, 2006;13:313–324.
5. Mitsuya H., Yarchoan R., Hayashi S., Broder S. (1990) Antiviral therapy against HIV infection. J Am Acad Dermatol, 1990; 22:1282– 1294.

6. Mitsuya H., Weinhold K.J., Furman P.A., St Clair M.H., Nusinoff- Lehrman S., Gallo R.C., Bolognesi D., Barry D.W., Broder S. (1985) 3¢-Azido-3¢-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III / lymphadenopathy-associated virus in vitro. Proc Natl Acad Sci USA, 1985; 82: 7096–7100.
7. Mitsuya H., Broder S. (1986) Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotrophic virus type III / lymphadenopathy-associated virus (HTLV-III / LAV) by 2¢,3¢-dideoxynucleosides. Proc Natl Acad Sci USA, 1986;83:1911–1915.
8. Yarchoan R., Mitsuya H., Thomas R.V., Pluda J.M., Hartman N.R., Perno C.F., Marczyk K.S., Allain J.P., Johns D.G., Broder S. (1989) In vivo activity against HIV and favorable toxicity profile of 2¢,3¢-dideoxyinosine. Science, 1989;245:412–415.
9. Coates J.A.V., Cammack N., Jenkinson H.J., Mutton I.M., Pearson B.A., Storer R., Cameron J.M., Penn C.R. (1992) The separated enantiomers of 2¢-deoxy-3¢-thiacytidine (BCH 189) both inhibit human immunodeficiency virus replication in vitro. Antimicrob Agents Chemother, 1992; 36: 202–205.
10. Baba M., Tanakas H., De Clercq E., Pauwels R., Balzarini J., Schols D., Nakashima H., Perno C.F., Walker R.T., Miyasaka T. (1989) Highly specific inhibition of human immunodeficiency virus type-1 by a novel 6-substituted acyclouridine derivative. Biochem Biophys Res Commun, 1989; 165: 1375–1381.
11. Pauwels R., Andries K., Desmyter J., Schols D., Kukla M.J., Breslin H.J., Raeymaeckers A., Van Gelder J., Woestenborghs R., Heykants J. (1990) Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives. Nature, 1990; 343:470–474.
12. Merluzzi V.J., Hargrave K.D., Labadia M., Grozinger K., Skoog M., Wu J.C., Shih C.K., Eckner K., Hattox S., Adams J. (1990) Inhibition of HIV-1 replication by a nonnucleoside reverse transcriptase inhibitor. Science, 1990; 250:1411–1413.
13. Romero D.L., Busso M., Tan C.K., Reusser F., Palmer J.R., Poppe S.M., Aristoff P.F., Downey K.M., So A.G., Resnick L., Tarpley W.G. (1991) Nonnucleoside reverse transcriptase inhibitors that potently and specifically block human immunodeficiency virus type 1 replication. Proc Nat Acad Sci, 1991; 88: 8806–8810.
14. Balzarini J., Pe¢ rez-Pe¢ rez M.J., San-Felix A., Schols D., Perno D.C.F., Vandamme A., Camarasa M.J., De Clercq E. (1992) 2¢,5¢- Bis-O-(tert-butyldimethylsilyl)-3¢-spiro-5¢¢-(4¢¢-amino-1¢¢,2¢¢-oxathiole-2¢¢,2¢-dioxide)pyrimidine (TSAO) nucleoside analogues:

highlyselective inhibitors of human immunodeficiency virus type 1 that are targeted at the viral reverse transcriptase. Proc Natl Acad Sci USA, 1992; 89: 4392–4396.

15. Pauwels R., Andries K., Debyser Z., Van Daele P., Schols D., Vandamme A.M., Janssen C.G.M., Anne J., Cauwenbergh G., Desmyter J., Heykants J., Janssen M.A.C., De Clercq E., Janssen P.A.J. (1993) Potent and highly selective human immunodeficiency virus type 1 (HIV-1) inhibition by a series of alphaanilinophenylacetamide derivatives targeted at HIV-1 reverse transcriptase. Proc Natl Acad Sci USA, 1993; 90: 1711–1715.
16. Kleim J.P., Bender R., Billhardt U.M., Meichsner C., Riess G., Rosner M., Winkler I., Paessens A. (1993) Activity of a novel quinoxaline derivative against human immunodeficiency virus type 1 reverse transcriptase and viral replication. Antimicrob Agents Chemother, 1993; 37: 1659–1664.
17. Ahgren C., Backro K., Bell F.W., Cantrell A.S., Clemens M., Colacino J.M., Deeter J.B., Engelhardt J.A., Hogberg M., Jaskunas S.R., Johanssons N.G. (1995) The PETT series, a new class of potent nonnucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase. Antimicrob Agents Chemother, 1995; 39:1329–1335.
18. Young S.D., Britcher S.F., Tran L.O., Payne L.S., Lumma W.C., Lyle T.A., Huff J.R., Anderson P.S., Olsen D.B., Carroll S.S. (1995) L-743, 726 (DMP-266): a novel, highly potent nonnucleoside inhibitor of the human immunodeficiency virus type 1 reverse transcriptase. Antimicrob Agents Chemother, 1995; 39: 2602– 2605.
19. Frank K.B., Noll G.J., Connell E.V., Sim I.S. (1991) Kinetic interaction of human immunodeficiency virus type 1 reverse transcriptase with the antiviral tetrahydroimidazo[4,5,1-jk]-[1,4]- benzodiazepine-2-(1H)-thione compound, R82150. J Biol Chem, 1991; 266: 14232–14236.
20. Althaus I.W., Chou J.J., Gonzales A.J., Deibel M.R., Chou K.C., Kezdy F.J., Romero D.L., Aristoff P.A., Tarpley W.G., Reusser F. (1993) Steady-state kinetic studies with the non-nucleoside HIV- 1 reverse transcriptase inhibitor U-87201E. J Biol Chem, 1993; 268: 6119–6124.
21. Spence R.A., Kati W.M., Anderson K.S., Johnson K.A. (1995) Mechanism of inhibition of HIV-1 reverse transcriptase by nonnucleoside inhibitors. Science, 1995; 267: 988–993.
22. Kohlstaedt L.A., Wang J., Friedman J.M., Rice P.A., Steitz T.A. (1992) Crystal structure at 3.5 A resolution of HIV-1 reverse transcriptase complexed with an inhibitor. Science, 1992; 256: 1783– 1790.
23. Smerdon S.J., Jager J., Wang J., Kohlstaedt L.A., Chirino A.J., Friedman J.M., Rice P.A., Steitz T.A. (1994) Structure of the binding site for nonnucleoside inhibitors of the reverse

transcriptase of human immunodeficiency virus type 1. Proc Natl Acad Sci USA, 1994; 91: 3911–3915.

24. Ren J.S., Esnouf R., Garman E., Jones Y., Somes D., Ross C., Kirby I., Keeling J., Darby G., Stuart D., Stammers D. (1995) High resolution structures of HIV-1 RT from four RT–inhibitor complexes. Nat Struct Biol, 1995; 2: 293–302.
25. Ding J., Das K., Tantillo C., Zhang W., Clark A.D.J., Jessen S., Lu X. et al. (1995) Structure of HIV-1 reverse transcriptase in a complex with the non-nucleoside inhibitor a-APA R 95845 at 2.8 _ resolution. Structure, 1995; 3: 365–379.
26. Ding J., Das K., Moereels H., Koymans L., Andries K., Janssen P.A.J., Hughes S.H., Arnold E. (1995) Structure of HIV-1 RT / TIBO R 86183 complex reveals similarity in the binding of diverse nonnucleoside inhibitors. Nat Struct Biol, 1995; 2: 407–415.
27. Ren J.S., Esnouf R., Hopkins A., Ross C., Jones Y., Stammers D., Stuart D. (1995) The structure of HIV-1 reverse transcriptase complexed with 9-chloro-TIBO: lessons for inhibitor design. Structure, 1995;3:915–926.
28. Smith M.S., Brian E.L., Pagano J.S. (1987) Resumption of virus production after human immunodeficiency virus infection of T lymphocytes in the presence of azidothymidine. J Virol; 61: 3769– 3773.
29. Vasudevachari M.B., Battista C., Lane H.C., Psallidopoulos M.C., Zhao B., Cook J., Palmer J.R., Romero D.L., Tarpley W.G., Salzman N.P. (1992) Prevention of the spread of HIV-1 infection with nonnucleoside reverse transcriptase inhibitors. Virology, 1992; 190: 269–277.
30. Balzarini J., Karlsson A., Pe¢rez-Pe¢rez M.J., Camarasa M.J., De Clercq E. (1993) Knocking-out concentrations of HIV-1-specific inhibitors completely suppress HIV-1 infection and prevent the emergence of drug-resistant virus. Virology, 1993;196:576–585.
31. Bacherler L., Jeffrey S., Hanna G., D'Aquila R., Wallace L., Logue K., Cordova B., Hertogs K., Larder B., Buckery R., Baker D., Gallagher K., Scarnati H., Tritch R., Rizzo C. (2001) Genotypic correlates of phenotypic resistance to efavirenz in virus isolates from patients failing nonnucleoside reverse transcriptase inhibitor therapy. J Virol;75:4999–5008.
32. Rodriguez-Barrios F., Balzarini J., Gago F. (2005)., J Am Chem Soc;127:7570–7578.
33. Miyasaka T., Tanaka H., Baba M., Hayakawa H., Walker R.T., Balzarini J., De Clercq E. (1989) A novel lead for specific anti- HIV-1 agents: 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. J Med Chem, 2005; 32: 2507–2509.

34. Hannongbuaa S., Pungpoa P., Limtrakula J., Wolschann P. (1999) Quantitative structure-activity relationships and comparative molecular field analysis of TIBO derivatised HIV-1 reverse transcriptase inhibitors. J Comput Aided Mol Des, 1999; 13: 563–577.
35. Garg R., Gupta S.P., Gao H., Babu M.K., Debnath A.K., Hansch C. (1999) Comparative quantitative structure–activity relationship studies on anti-HIV drugs. Chem Rev, 1999; 99: 3525–3601.
36. Roy K., Leonard J.T. (2004) QSAR modeling of HIV-1 reverse transcriptase inhibitor 2-amino-6-arylsulfonylbenzonitriles and congeners using molecular connectivity and E-sate parameters. Bioorg Med Chem, 2004; 12: 745–754.
37. Gayen S., Debnath B., Samanta S., Jha T. (2004) QSAR study on some anti-HIV HEPT analogues using physicochemical and topological parameters. Bioorg Med Chem, 2004; 12: 1493–1503.
38. Juan A.A.S. (2008) 3D-QSAR models on clinically relevant K103N mutant HIV-1 reverse transcriptase obtained from two strategic considerations. Bioorg Med Chem Lett, 2008; 18: 1181–1194.
39. Hua R., Doucet J.P., Delamar M., Zhang R. (2009) QSAR models for 2-amino-6-arylsulfonylbenzonitriles and congeners HIV-1 reverse transcriptase inhibitors based on linear and nonlinear regression methods. Eur J Med Chem, 2009; 44: 2158–2171.
40. Sabet R., Fassihi A., Moeinifard B. (2009) QSAR study of PETT derivatives as potent HIV-1 reverse transcriptase inhibitors. J Mol Graph Model, 2009; 28: 146–155.
41. Hu R., Barbault F., Delamar M., Zhang R. (2009) Receptor- and ligand-based 3D-QSAR study for a series of non-nucleoside HIV-1 reverse transcriptase inhibitors. Bioorg Med Chem, 2009; 17: 2400–2409.
42. Cichero E., Cesarini S., Fossa P., Spallarossa A., Mosti L. (2009) Thiocarbamates as non-nucleoside HIV-1 reverse transcriptase inhibitors: docking-based CoMFA and CoMSIA analyses. Eur J Med Chem, 2009; 44: 2059–2070.
43. Chiu T.-L., So S.-S. (2004) Development of neural network QSPR models for hansch substituent constants. 2. applications in QSAR studies of HIV-1 reverse transcriptase and dihydrofolate reductase inhibitors. J Chem Inf Comput Sci, 2004; 44: 154–160.
44. Cramer R.D. III, Patterson D.E., Bunce J.D. (1988) Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins. J Am Chem Soc, 1988; 110: 5959–5967.

45. Garg R., Kurup A., Gupta S.P. (1997) Quantitative structure-activity relationship studies on some acyclouridine derivatives acting as anti-HIV-1 drugs. Quant Struct-Act Rel, 1997;16: 20–24.
46. Luco J.M., Ferretti F.H. (1997) QSAR based on multiple linear regression and PLS methods for the anti-HIV activity of a large group of hept derivatives. J Chem Inf Comput Sci; 37: 392–401.
47. Goodsell D.S., Morris G.M., Olson A.J. (1996) Automated docking of flexible ligands: applications of autodock. J Mol Recognit, 1996; 9:1–5.
48. Morris G.M., Huey R., Olson A.J. (2008) Using AutoDock for ligand–receptor docking. In: Current Protocol in Bioinformatics. Malden, MA: John Wiley & Sons, Inc.; 14 p, chapter 8; unit 8.
49. Trott O., Olson A.J. (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem, 2008; 31: 455–461.
50. Insight-II, version (2005) molecular modelling package, and Del- Phi version 30 solvation program, 2000. San Diego, CA: Accelrys, Inc.
51. Wold S., Rhue A., Wold H., Dunn W.J. III (1984) The collinearity problem in linear regression. the partial least squares (PLS) approach to generalized inverses. SIAM J Sci Stat Comput, 1984; 5:735–743.
52. Wold S. (1991) Validation of QSAR's. Quant Struct-Act Rel, 1991; 10: 191–193.
53. Clark M., Cramer R.D. III (1993) The probability of chance correlation using partial least squares (PLS). Quant Struct-Act Rel, 1993; 12: 137–145.
54. Tanaka H., Takashima H., Ubasawa M., Sekiya K., Nitta I., Baba M., Shigeta S., Walker R.T., De Clercq E., Miyasaka T. (1992) Synthesis and antiviral activity of deoxy analogs of 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)thymine (HEPT) as potent and selective anti-HIV-1 agents. J Med Chem, 1992; 35: 4713–4719.