Acta Pharm. **59** (2009) 31–43
10.2478/v10007-009-0006-y

Original research paper

Investigation of the structural requirement for inhibiting HIV integrase: QSAR study

NIGUS DESSALEW*

Department of Pharmaceutical Chemistry School of Pharmacy Addis Ababa University P.O. Box 1176, Addis Ababa Ethiopia

HIV integrase has emerged as a promising target for discovery of agents against the acquired immunodeficiency syndrome (AIDS) pandemic. With the purpose of designing new chemotypes with enhanced potencies against the HIV integrase enzyme, the QSAR study carried out on 37 novel phthalimide derivatives is presented. The developed QSAR model was validated by standard statistical parameters and through a detailed structural study of how it reproduces and explains the quantitative differences seen in experimentally known pharmacological data. The model showed a good correlative and predictive ability having a cross-validated correlation coefficient (r^2_{cv}) of 0.709 and a conventional correlation coefficient (r^2) of 0.949. The predictive correlation coefficient (r^2_{pred}) was found to be 0.512. The study revealed that the antiretroviral activity is predominantly explained by the substituent size, shape and polarity and provided insights into how modulation of the steric bulkiness and polarities of the substituents could be made to optimize the integrase-inhibitor interaction chemistry. A detailed investigation was made of the structural basis for the antiretroviral activity and the findings from the study could be usefully employed to design antagonists with a much more enhanced potency and selectivity.

Keywords: QSAR, HIV/AIDS, integrase, phthalimides, TSAR

Accepted January 19, 2009

Human immunodeficiency virus (HIV) currently affects some 50 million people around the globe. Although the development of combination antiretroviral therapy has provided a clinically useful method of suppressing the viremia in infected individuals, there are currently no curative therapies for the HIV/AIDS pandemic (1). Moreover, the complexity of the dosing regimens, the unbearable toxicity of the available antiretroviral

* Correspondence; e-mail: dnigus@phar.aau.edu.et, nigusd96@yahoo.com

therapies and the increasing retroviral resistance to the currently available drugs means that there is an urgent need to identify novel structural classes of agents with improved efficacy and safety (2, 3).

HIV-1 integrase (IN), the enzyme responsible for the integration of viral DNA into the host genome, represents an attractive, yet unexploited, target for the treatment of HIV infection. It is an important chemotherapeutic target because no mammalian counterpart to this enzyme has been identified, and the region of the HIV pol gene encoding IN shows more conservation than the reverse transcriptase and protease encoding regions (4). IN is active in both the cytoplasm and nucleus of the host cell, while in the cytoplasm IN forms a pre-integration complex with viral DNA and selectively cleaves 3′--terminal dinucleotides from each end (5). This so-called 3′-processing event occurs prior to nuclear translocation of the complex. In the nucleus, IN catalyzes strand transfer, which leads to integration of viral DNA into the host DNA (6). The latter process is essential for viral replication. Given the importance of DNA integration for the viral life cycle, HIV integrase has become one of the most promising targets and has attracted attention for the discovery and development of agents against the AIDS pandemic (7, 8).

Tools for Structure Activity Relationships (TSAR) is a package for interactive investigation of quantitative structure-activity relationships (9). Like all QSAR methods (10-12), it is based on a numerical description of molecular structure and employs statistics to obtain quantitative correlation. Molecular structures are represented with a variety of 2D and 3D descriptors, the activity-descriptor relationship is computed by different standard statistical tools such as multiple regression, partial least square regression and neural network analysis, and the output is displayed in the form of a model highlighting substituent points that are strongly correlated with the pharmacotoxicological properties under investigation. The methodology assumes that suitable sampling of these structural descriptors provides all the information needed for understanding their biological properties. It has been used to investigate the structural requirement for activity on dif-

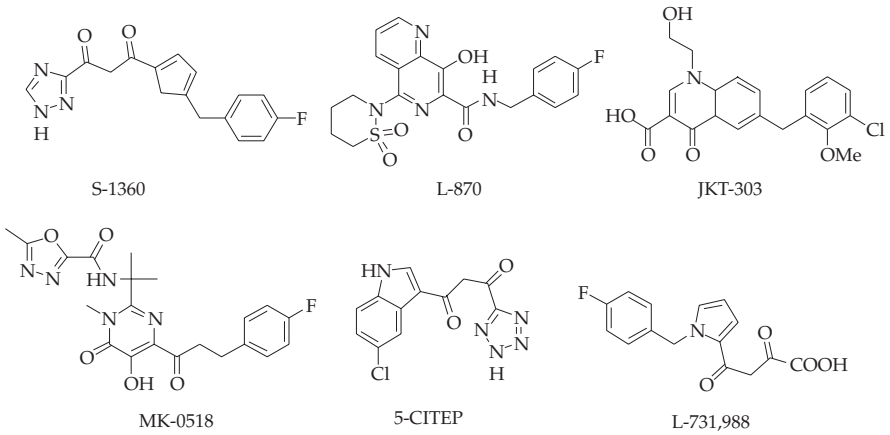


Fig. 1. Examples of HIV integrase inhibitors.

ferent receptors (13). These tools may attest the usefulness of such methodology for understanding the structural requirements for pharmacological properties of a given series.

Intense research on small molecule inhibitors of HIV integrase has produced a diverse class of chemical scaffolds (14, 15). Fig. 1 shows some integrase inhibitors. Although diverse in structure and large in number, there is currently no drug that acts on the enzyme and, in fact, most of the known inhibitors are beset with the problem of toxicity, non-selectivity and weak binding affinity. In common with other QSAR tools, TSAR is generally employed to enhance and optimize the binding affinity using a series of compounds acting on the same target with the same mechanism of action. Information about the structural requirements for the observed biological properties aids to design a new entity having an acceptable level of potency and selectivity. In this paper, we report the QSAR study carried out on 37 novel integrase antagonists aimed at getting a model that would account for the quantitative differences in bioactivity seen in this series and using the findings to design ligands with pronounced inhibitory potency and selectivity.

EXPERIMENTAL

Dataset for analysis

The *in vitro* biological activity data reported as pIC_{50} for inhibition of HIV integrase by a series of phthalimide derivatives (16) was used as a dependent variable for the TSAR study. The integrase activity was determined using an oligonucleotide-based assay in which the DNA strand transfer by preformed complexes of integrase and processed DNA was measured by means of an ELISA test in microtiter plate format using recombinant His--tagged HIV-1 integrase produced in the *Escherichia coli* strain BL21(DE3). HPLC-purified oligonucleotides were used for the preparation of viral DNA substrate and target DNA. For the integration strand transfer reactions, a 20 nmol L^{-1} biotinylated DNA substrate was preincubated with 300 nmol L^{-1} HIV integrase at 37 °C for 5 min. On the basis of the calculated percent inhibition for each compound concentration, dose-response curves were plotted and pIC_{50} values were calculated.

Molecular modeling

Structures of the phthalimide derivatives selected for the present QSAR study were sketched using the ChemDraw ultra 8.0 and exported to the TSAR 3.3 software (Accelrys, Oxford Molecular Limited, Oxford 2000). Three-dimensional structures of all molecules were generated and partial charges were derived using the Charge-2 CORINA 3D package in TSAR 3.3 and the inhibitor geometries were optimized using its Cosmic module. Calculations were terminated when the energy difference or energy gradient were smaller than 1×10^{-5} and 1×10^{-10} kcal mol^{-1}, respectively. Molecular descriptors were obtained for the substituents, which vary in common points of the generic structure. TSAR allow calculation of the following descriptors: molecular surface area and volume, moments of inertia, ellipsoidal volume, verloop parameters, dipole moments, lipole moments, molecular mass, Wiener index, molecular connectivity indices, molecular shape indices, electrotopological state indices, log *P*, number of defined atoms (carbon, nitrogen, *etc.*),

rings (aromatic and aliphatic), and groups (methyl, hydroxyl, *etc.*). Vamp, which is a semiempirical molecular orbital package in TSAR 3.3, was used to calculate the electrostatic properties such us total energy, electronic energy, nuclear repulsion energy, accessible surface area, atomic charge, mean polarizability, heat of formation, HOMO and LUMO eigenvalues, ionization potential, total dipole, polarizability, and dipole components. Structure optimization was performed *in vacuo* using default parameters with the AM1 Hamiltonian. Pairwise correlation analysis of the calculated descriptors was performed. The model was obtained using descriptors that are strongly correlated with the HIV entry blocking activity.

Statistical analysis

The relationship between structural parameters and biological activities was quantified by the multiple linear regressions implemented in TSAR 3.3. Values for *F*-to-enter and *F*-to-leave were set to 4. The cross-validation analysis was performed using the leave-one-out (LOO) method where one compound is removed from the dataset and its activity is calculated using the model derived from the rest of the dataset. The cross-validated r^2 and conventional r^2 that resulted in the lowest error of prediction were chosen. Unless otherwise stated, the default values for the other QSAR parameters were used.

Predictive correlation coefficient (r^2_{pred})

The predictive capability of the 2D-QSAR models was determined from a set of nine compounds that were separated during model development. Structure generation, optimization, charge derivation, and all other steps of test sets were done in the same way as that of the training set compounds as described above, and their activities were calculated using the model produced by the training set.

The predictive correlation (r^2_{pred}), based on the test set molecules, is computed using:

$$r^2_{\text{pred}} = (\text{SD-PRESS})/\text{SD}$$

where SD is the sum of squared deviations between biological activities of the test set and mean activities of the training set molecules and the predictive residual sum of squares (PRESS) is the sum of squared deviations between calculated and experimental activity values for every molecule in the test set.

RESULTS AND DISCUSSION

The QSAR study was carried out using phthalimide analogues reported to be novel integrase inhibitors. Molecules that lack biological activity in numerical form were removed from the analysis. Following this, 37 molecules were left for the present study. The remaining dataset was randomly partitioned into a training set of 28 and a test set of 9 compounds with bias given to both chemical and biological diversity in both the

training and test set molecules. Despite the ambiguity of drug-receptor interaction in general, a statistically significant model was obtained from the study.

The TSAR multiple regression analysis is summarized in Table I. The cross-validated correlation coefficient defines the goodness of prediction whereas the non-cross-validated conventional correlation coefficient indicates the goodness of fit of a QSAR model. The *F*-test value stands for the degree of statistical confidence. As evident from the table, a cross-validated correlation coefficient of 0.709 was obtained using the leave-one-out cross-validation procedure. This indicates the very good internal predictive capability of the developed model. The model also exhibited a non-cross validated correlation coefficient of 0.949. The high value of this parameter adds to its usefulness as a predictive tool. The external predictive capability of a QSAR model is generally checked using test sets. All the procedures, including geometry optimization, charge computation, calculation of structural descriptors of the nine test set molecules, were done in a manner identical to the training set molecules. A predictive correlation coefficient of 0.512 was obtained from the study, indicating the usefulness of the developed QSAR in predicting activities of molecules not included in its derivation. Another way to further evaluate the significance of the developed model is to test it for statistical stability. To this end, the standard error of estimate and predictive residual sum of squares may be employed. Low values of the standard error of estimate (0.152) and of PRESS for the training (0.496) and test sets (0.629) further add to the statistical significance of the developed models.

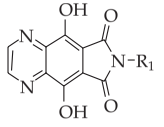
Structures of the inhibitors chosen and the experimental and calculated activity are displayed in Table II. Fig. 2 shows plots of experimental *vs.* calculated pIC_{50} values for both the training and test set molecules. Histograms of the residuals of the test set molecules are presented in Fig. 3 being a plot of residuals against observations, each observation representing the data for a single structure. These two plots are important to graphically observe the predictive capability of QSARs. Shorter heights of the residuals and the

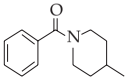
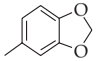
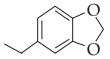
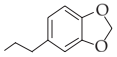
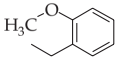
Table I. Statistical parameters obtained for the TSAR model

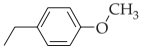
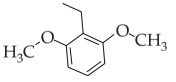
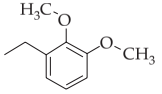
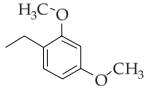
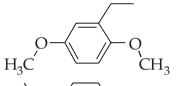
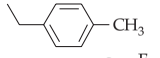
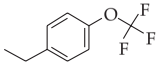
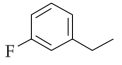
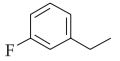
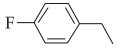
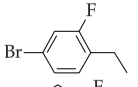
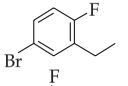
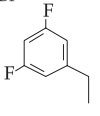
QSAR parameter	
No. of molecules in the training set	28
No. of molecules in the test set	9
r^2_{cv}	0.709
r^2	0.949
SEE	0.152
F-value	65.11
F-probabilty	8.69644e-015
PRESS[a]	0.496
PRESS[b]	0.629
r^2_{pred}	0.512

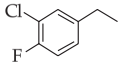
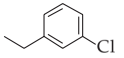
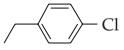
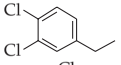
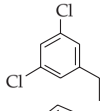
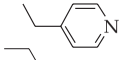
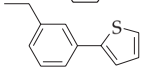
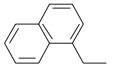
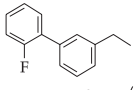
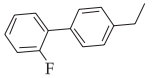
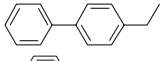
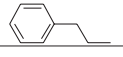
r^2_{cv} – cross-validated correlation coefficient; r^2 – conventional correlation coefficient; SEE – standard error of estimate; r^2_{pred} – predictive correlation coefficient
PRESS[a] – predictive residual sum of squares for the training set; PRESS[b] – predictive residual sum of squares for the test set molecules.

Table II. Structures of antagonists used for QSAR analysis with the corresponding experimental and calculated activities



Compd.	R_1	Experimental pIC_{50}	Calculated pIC_{50}	Residual	Verloop L	Verloop B1	Total dipole moment	MR	Sloppiness	
									Balaban	Wiener
1		6.68	6.48	0.20	4.986	1.650	2.354	37.932	1.876	61
2	CH_3–	4.31	4.31	0.00	3.106	1.650	0.130	5.697	0.00	0.00
3		4.98	5.04	–0.06	5.198	1.910	0.405	22.109	2.022	15
4		5.62	5.70	–0.08	10.430	1.650	5.628	60.409	1.809	378
5		5.66	5.77	–0.11	6.251	1.650	1.333	31.442	2.123	42
6		5.98	5.79	0.19	4.789	1.938	1.279	34.728	2.125	64
7		5.69	5.83	–0.14	4.660	1.934	1.282	34.728	2.125	64
8		5.00	5.00	0.00	7.311	1.704	0.373	31.091	1.928	79
9t		6.25	5.92	0.33	5.666	1.650	1.978	35.926	1.932	108
10t		5.85	5.82	0.03	9.645	1.902	2.149	40.681	1.886	147
11		6.09	5.99	0.10	5.049	1.650	0.461	36.773	2.297	86

12		6.25	5.95	0.30	6.894	1.650	2.408	36.773	2.180	90
13		5.70	5.70	0.00	7.186	1.702	1.137	43.236	2.446	150
14t		6.37	6.57	–0.20	8.106	1.650	1.092	43.236	2.484	148
15		6.37	6.26	0.11	5.377	1.650	1.780	43.236	2.374	154
16		6.11	6.06	0.05	5.911	1.650	1.473	43.236	2.345	156
17		5.80	6.17	–0.37	5.338	1.650	1.540	35.350	2.192	62
18		5.69	5.61	0.08	7.161	1.650	3.594	36.852	2.264	207
19		6.37	6.5	–0.13	4.661	1.650	3.730	36.283	2.461	148
20		6.25	6.32	–0.07	4.526	1.650	2.604	30.526	2.231	61
21		6.38	6.31	0.07	4.876	1.650	3.004	30.526	2.192	62
22		6.36	6.44	–0.08	5.360	1.650	2.353	38.149	2.346	84
23		6.45	6.36	0.09	4.718	1.650	1.360	38.149	2.346	84
24		6.43	6.33	0.10	4.585	1.650	3.038	30.742	2.341	84

25		6.75	6.76	–0.01	4.820	1.650	4.060	35.330	2.346	84
26		6.66	6.56	0.10	4.600	1.650	2.685	35.114	2.231	61
27		6.38	6.51	–0.13	5.259	1.650	3.088	35.114	2.192	62
28		6.95	6.93	0.02	5.272	1.650	4.092	39.919	2.346	84
29		6.73	6.71	0.02	5.324	1.650	3.108	39.919	2.341	84
30		6.20	6.40	–0.20	4.939	1.650	1.375	37.932	2.279	60
31t		5.17	5.53	–0.36	4.414	1.650	3.815	28.121	2.123	42
32t		5.85	5.77	0.08	8.350	1.650	1.554	46.760	1.993	140
33t		6.17	6.47	–0.30	4.496	1.650	2.155	59.034	1.727	259
34t		6.30	6.52	–0.22	4.732	1.650	2.801	55.662	1.911	294
35		6.00	6.03	–0.03	6.346	1.650	2.408	55.662	1.867	301
36t		5.84	6.21	–0.37	6.770	1.650	2.737	55.446	1.789	252
37t		5.69	5.43	0.26	8.421	1.688	1.704	35.064	2.125	64

Compound numbers with 't' denote compounds included in the test set molecules.
MR is the molar refracrtivity.

fact that the training set molecules are on or near the best fit line, as shown in Fig. 2, further add to the usefulness of the developed QSAR. Table III shows the descriptors included in the final QSAR model and their statistical significance.

The QSAR model with high statistical significance is represented by Eq. (*1*):

$$p\mathit{IC}_{50} = -0.221X1 - 1.29X2 + 0.217X3 + 0.057X4 + 0.297X5 - 0.005X6 + 6.772 \quad (1)$$

where X1 is the Verloop length parameter, X2 is Verloop B1, X3 is the total dipole moment, X4 is the molar refractivity, X5 is the Balaban topological index and X6 is the Wiener topological index of the substituents at R1.

The statistics for Eq. (*1*) is shown in Table I. As the QSAR shows, the integrase inhibitory activity improves with an increase in the total dipole moment, molar refractivity and the Balaban topological index parameter of substituents at position R1 while the antagonistic activity was found to decrease with an increase in the values of the Verloop substituent length and width steric parameter and Wiener's topological index. The

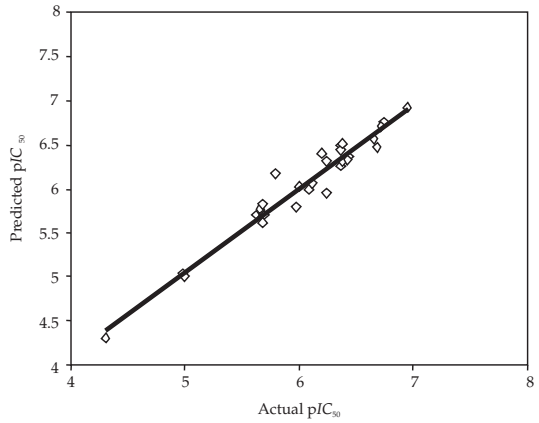


Fig. 2. Plot of experimental *vs.* calculated pIC_{50} values for training set molecules.

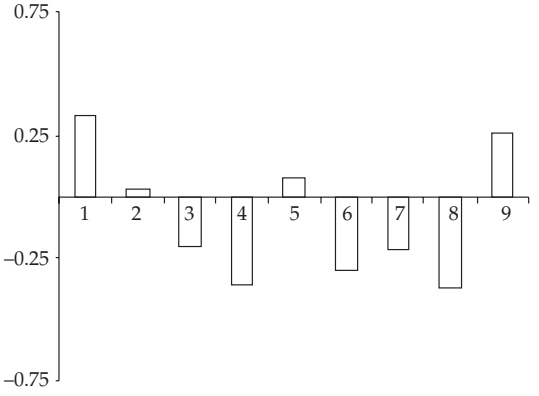


Fig. 3. Histogram of residuals between the actual and predicted pIC_{50} values of the test set molecules.

Table III. Statistical significance of parameters X1 through X6 in the TSAR–derived model describing the antiretroviral activity of phthalimide analogues

Structural descriptor	Code	Regression coefficient[a]	Jacknife SE[b]	Covariance SE[c]	*t*-value[d]	*t*-probability[e]
Verloop L	X1	–0.224	0.041	0.033	–6.645	1.41×10^{-6}
Verloop B1	X2	–1.290	0.552	0.366	–3.527	2.0×10^{-3}
Total dipole moment	X3	0.217	0.027	0.029	7.483	2.36×10^{-7}
MR	X4	0.057	0.009	0.0079	7.273	3.66×10^{-7}
Balaban topological index	X5	0.297	0.110	0.099	3.007	7×10^{-3}
Wiener topological index	X6	–0.0054	0.001	0.001	–5.286	3.06×10^{-5}
Constant	C	6.772	0.921			

[a] The regression coefficient for each variable in the equation.
[b] An estimate of the standard error of each regression coefficient derived from a jack-knife procedure on the final regression model.
[c] Estimate of the standard error of each regression coefficient derived from the covariance matrix.
[d] Significance of each variable included in the final model.
[e] Statistical significance for *t*-values.
MR – molar refractivity.

Verloop parameters (17–19) are a set of multi-dimensional steric descriptors defining a box that can be used to characterize the shape and volume of the substituent, which are very important in explaining the steric influence of substituents in the interaction of organic compounds with macromolecular drug receptors. The Verloop B1-B5 parameters describe the width of the substituent in the direction perpendicular to the length of the substituent. That Verloop's length parameter of substituents at position R1 is negatively correlated with the inhibitory activity is what appears to explain the better activities of compound **34** compared to compound **35**, compound **15** compared to compound **16**. In both cases, more active molecules (compounds **34** and **15**) has a substituent leaving a lower value of the negatively correlated length descriptor. The dimethoxy groups in compound **15** are *meta* substituted whereas in compound **16** the moieties are in a *para* relationship, which apparently increased the length of the substituent which is negatively related to integrase inhibitory activity. The same reasoning seems to apply for the better activity of compound **35** compared to compound **34**: the fluorophenyl ring in compound **35** is in *para* position to the benzyl ring whereas it is in *meta* position in compound **34**, which contributes to the higher activity, since the length descriptor for the whole substituent is now smaller because of differences in the relative positioning of the fluorophenyl ring in both compounds. Better activity of compound **26** compared to compound **27**, compound **28** compared to compounds **22**, **37** can be explained on the same ground. In each case, a more active inhibitor has a lower value for the negatively related length parameter and a higher value for the positively correlated total dipole moment of substituents. The QSAR shows that the Verloop B1 descriptor is better related to activity than the other descriptors, which is evident from the higher value of B1 descriptor coefficient

(1.29). The study suggests that the integrase inhibitory activity exhibited is explained by steric factors and polarity of substituents and that for improved activity, substituents with less steric bulkiness and more polarity are desired. Considering the fact that the 2D-QSAR model was able to reproduce the experimental facts and that it was validated by appropriate statistical procedures, it could be useful in designing a more potent inhibitor.

CONCLUSIONS

HIV integrase have emerged as an important drug target with a huge therapeutic potential for its inhibitors. The QSAR analysis using 37 phthalimide derivatives was successfully carried out to build a statistically significant model possessing a good correlative and predictive capability for inhibition of the HIV integrase enzyme. The 2D-QSAR model was validated by standard statistical means to check how it reproduces and explains the differences in the experimentally known activity data. Detailed structural investigation revealed that the antiretroviral activity is predominantly explained by substituent size, shape and polarity and provided insights into how modulation of the steric bulkiness and polarity of the substituents could be useful to optimize the integrase-inhibitor binding chemistry and hence improve the observed biological activity. This analysis could help rational design of potential drug candidates with enhanced inhibitory potency.

REFERENCES

1. D. Finzi, J. Blankson, J. D. Siliciano, J. B. Margolick, K. Chadwick, T. Pierson, K. Smith, J. Lisziewicz, F. Lori, C. Flexner, T. C. Quinn, R. E. Chaisson, E. Rosenberg, B. Walker, S. Gange, J. Gallant and R. F. Siliciano, Latent infection of CD4 T cells provides a mechanism for lifelong persistence of HIV-1, *Nat. Med.* **5** (1999) 512–517; DOI: 10.1038/8394.
2. S. G. Deeks, M. Smith, M. Holodniy and J. O. Kahn, HIV-1 protease inhibitors. A review for clinicians, *JAMA* **277** (1997) 145–153; DOI: 10.1001/jama.277.2.145.
3. J. Martinez-Picado, M. P. DePasquale, N. Kartsonis, G. J. Hanna, J. Wong, D. Finzi, E. Rosenberg, H. F. Günthard, L. Sutton, A. Savara, C.J. Petropoulos, N. Hellmann, B. D. Walker, D. Richman, R. Siliciano and R. T. D'Aquila, Antiretroviral resistance during successful therapy of HIV type 1 infection, *Proc. Natl. Acad. Sci. USA* **97** (2000) 10948–10953.
4. C. L. Kuiken, B. Foley, B. Hahn, P. A. Marx, F. McCutchan, J. Mellors, J. Mullins, S. Wolinsky and B. Korber, *HIV Sequence Compendium 2000*, Theoretical Biology and Biophysics Group, Los Alamos National Labatory: Los Alamos, Wiley, New York 2000.
5. P. O. Brown, *Integration*, in *Retroviruses* (Eds. J. M. Coffin, S. H. Hughes and H. E. Varmus), Cold Spring Harbor Laboratry Press, Cold Spring Harbor, New York 1997, pp. 161–203.
6. E. Asante-Appiah and A. M. Skalka, HIV-1 integrase: structural organization, conformational changes, and catalysis, *Adv. Virus Res.* **52** (1999) 351–369; DOI: 10.1016/S0065-3527(08)60306-1.
7. N. J. Anthony, HIV-1 integrase: a target for new AIDS chemotherapeutics, *Curr. Top. Med. Chem.* **4** (2004) 979–990; DOI: 10.2174/1568026043388448.
8. T. K Chiu and D. R. Davies, Structure and function of HIV-1 integrase, *Curr. Top. Med. Chem.* **4** (2004) 965–977; DOI: 10.2174/1568026043388547.

9. A. Kovatcheva, G. Buchbauer, A. Golbraikh and P. Wolschann, QSAR modeling of alpha-campholenic derivatives with sandalwood odor, *J. Chem. Inf. Comput. Sci.* **43** (2003) 259–266; DOI: 10.1021/ci020296n.
10. N. Dessalew and P. V. Bharatam, 3D-QSAR and molecular docking study on bisarylmaleimide series as glycogen synthase kinase 3, cyclin dependent kinase 2 and cyclin dependent kinase 4 inhibitors: An insight into the criteria for selectivity, *Eur. J. Med. Chem*. **42** (2007) 1014–1027; DOI: 10.1016/j.ejmech.2007.01.010.
11. N. Dessalew, D. S. Patel and P. V Bharatam, 3D-QSAR and molecular docking studies on pyrazolopyrimidine derivatives as glycogen synthase kinase-3b inhibitors, *J. Mol. Graph. Mod*. **25** (2007) 885–895; DOI: 10.1016/j.jmgm.2006.08.009.
12. N. Dessalew, P. V. Bharatam and S. K. Singh, 3D-QSAR CoMFA study on aminothiazole derivatives as cyclin-dependent kinase 2 inhibitors, *QSAR Comb. Sci.* **26** (2007) 85–91; DOI: 10.1002/qsar.200630032.
13. N. Dessalew, QSAR study on aminophenylbenzamides and acrylamides as histone deacetylase inhibitors: An insight into the structural basis of antiproliferative activity, *Med. Chem. Res*. **7** (2008), 449–460; DOI: 10.1007/s00044-007-9085-9.
14. D. C. Meadows, T. B. Mathews, T. W. North, M. J. Hadd, C. L. Kuo, N. Neamati and J. Gervay-Hague, Synthesis and biological evaluation of geminal disulfones as HIV-1 integrase inhibitors, *J. Med. Chem.* **48** (2005) 4526–4534; DOI: 10.1021/jm049171v.
15. J. A. Grobler, K. Stillmock, B. Hu, M. Witmer, P. Felock, A. S. Espeseth, A. Wolfe, M. Egbertson, M. Bourgeois, J. Melamed, J. S. Wai, S. Young, J. Vacca and D. J. Hazuda, Diketo acid inhibitor mechanism and HIV-1 integrase: implications for metal binding in the active site of phosphotransferase enzymes, *Proc. Natl. Acad. Sci. USA* **99** (2002) 6661–6666; DOI: 10.1073/pnas.092056199.
16. W. G. Verschueren, I. Dierynck, I. E. Katie, L. Hu, M. J. Paul, G. Boonants, M. E. Pille, F. D. Frits, K. Hertogs, L. N. Dominique, G. Surleraux, B. T. Piet and P. Wigerinck, Design and optimization of tricyclic phtalimide analogues as novel inhibitors of HIV-1 Integrase, *J. Med. Chem.* **48** (2005) 1930–1940; DOI: 10.1021/jm049559q.
17. A. Verloop, W. Hoogenstraaten and J. Tipker, Development and Application of new Steric Substituent Parameters, *in Drug Design* (Ed. E. J. Ariens), Academic Press, New York 1976, pp. 165–207.
18. A. Verloop and J. Tipker, Use of linear free energy related and other parameters in the study of fungicidal selectivity, *Pest. Sci.* **7** (1976) 379–390.
19. Verloop and J. Tipker, A comparative study of new parameters in drug design, in *Biological Activity and Chemical Structure* (Ed. J. A. Keverling Buisman), Elsevier, Amsterdam 1977, pp. 63–81.

S A Ž E T A K

Istraživanje strukturnih značajki inhibitora HIV integraze prema QSAR studiji

NIGUS DESSALEW

HIV integraza se pokazala kao ciljni enzim u istraživanju lijeka protiv AIDS pandemije. Sa ciljem pronalaženja strukturnih značajki nužnih za inhibiciju HIV integraze, provedena su QSAR istraživanja na 37 novih derivata ftalimida. Razvijeni QSAR model je validiran standardnim statističkim parametrima. Detaljno je proučavano kako promjene u strukturi utječu na kvantitativne razlike u farmakološkom djelovanju. Model je pokazao dobru korelaciju i sposobnost predikcije, uz križno validiran koeficijent korelacije

(r^2_{cv}) 0,709, koeficijent korelacije (r^2) 0.949 i relativni koeficijent predikcije (r^2_{pred}) 0,512. Istraživanja pokazuju da na virustatsko djelovanje prije svega utječu veličina, oblik i polarnost supstituenta te ukazuju na poželjne steričke i strukturne promjene koje bi mogle doprinjeti optimizaciji inhibitora HIV integraze. Rezultati istraživanja mogli bi biti korisni za dizajniranje antagonista s mnogo naglašenijom djelotvornošću i selektivnošću.

Ključne riječi: QSAR, HIV/AIDS, integraza, ftalimidi, TSAR

Department of Pharmaceutical Chemistry, School of Pharmacy, Addis Ababa University, P.O. Box 1176 Addis Ababa, Ethiopia