Asian Journal of Chemistry Vol. 19, No. 5 (2007), 4110-4112

NOTE

QSAR Analysis of 5,6-Dihydro-4-hydroxy-2-pyrone Analogues: HIV-1 Protease Inhibitor

MEENAKSHI JAISWAL, RICHA MISHRA, BRIJESHKUNVAR MISHRA* and N.S. HARI NARAYANA MOORTHY
School of Pharmaceutical Sciences, UTD
Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal-462 036, India
E-mail: brijeshkunvar_mishra@yahoo.com

A series of 17 compound containing 6-phenyl-6-phenethyl dihydropyrone derivatives that are HIV-1 protease inhibitors has been selected for QSAR analysis by using physico-chemical and indicator variables. For enzyme activity, the result obtained from the regression analysis shows that biological activity positively correlates with the molar refractivity and negatively correlates with the F and the R_2 descriptors. For cellular toxicity the hydrogen acceptor and σ_m/σ_p correlates positively and molar refractivity negatively correlates with the biological activity. The model 1 developed for predicting the activity has 95 % significance and the correlation coefficient (r = 0.779) and test for significance (F = 6.724) indicate very good predictive ability.

Key Words: QSAR, 5,6-Dihydro-4-hydroxy-2-pyrone.

Acquired immuno deficiency syndrome (AIDS) is a systemic and fatal disorder produced by the human immuno deficiency virus (HIV) which is retrovirus of the lentivirus family and causes destruction and/or functional impairment of cells of the immune-system, particularly CD^{4+} T-cells. HIV progressively destroys the body's ability to fight infections[1]. HIV-1 protease plays an important role in the post translational processing of gag and gag-pol viral gene products and thereby is essential for virion maturation. Protease inhibitors inhibit the ability of a particular protease to break the peptide bonds within a given protein[2]. The majority of the HIV protease inhibitors reported are peptidic or peptidomimetic in nature. Peptidic compounds are known to possess pharmacological problems such as biliary excretion and low bioavaibility[3]. Adequate supplies of these agents have been limited by the synthetic difficulties associated with large compounds containing multiple chiral centers. Therefore, there is a need for small non peptide HIV-1 protease inhibitors that are easy to synthesize, exhibit good bioavailability and preferably have unique pattern of resis-

tance development. A nonpeptidic 5,6-dihydro-4-hydroxy-2-pyrone low molecular weight compound, reported to possess potent HIV-1 protease inhibitory activity was selected for QSAR study (Fig. 1).

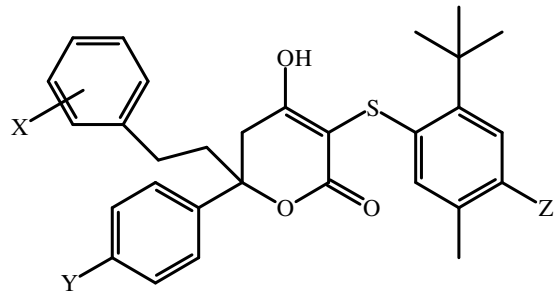

Fig. 1. Parent structure of 6-phenyl-6-phenethyldihydropyrones

TABLE-1
HIV-1 PROTEASE INHIBITORY ACTIVITY OF
6-PHENYL-6-PHENETHYLDIHYDROPYRONES

Comp. No.	X	Y	Z	IC_{50} (μm)	TC_{50} (μm)	-log IC_{50}	-log TC_{50}
1	H	H	H	35.0	55	-1.5442	-1.7402
2	H	H	OH	33.0	23	-1.5185	-1.3617
3	H	H	$O(CH_2)_2OH$	6.8	20	-0.8322	-1.3010
4	H	H	CH_2OH	6.6	66	-0.8195	-1.8195
5	H	H	OCH_3	15.0	33	-1.1762	-1.5185
6	4-OH	H	H	11.0	69	-1.0412	-1.8388
7	4-NH_2	H	H	24.0	54	-1.3802	-1.7323
8	H	OH	H	40.0	23	-1.6020	-1.3617
9	H	NH2	H	32.0	67	-1.5051	-1.8260
10	H	$O(CH_2)_2OH$	H	12.0	23	-1.0795	-1.3617
11	4-OH	H	CH_2OH	1.7	>100	-0.2308	>100
12	3-OH	H	CH_2OH	2.5	>100	-0.3976	>100
13	4-NH_2	H	CH_2OH	3.1	94	-0.4913	-1.9731
14	3-NH_2	H	CH_2OH	4.0	23	-0.6020	-1.3617
15	H	$O(CH_2)_2OH$	CH_2OH	1.4	67	-0.1461	-1.8260
16	H	$O(CH_2)_2OH$	$O(CH)_2OH$	6.4	25	-0.8061	-1.3979
17	H	$O(CH_2)_2OH$	OH	3.7	27	-0.5685	-1.4313
18	H	$O(CH_2)_2OH$	CH_2OCH_3	4.5	18	-0.6535	-1.2552
19	4-OH	OH	CH_2OH	120.0	21	-2.0792	-1.3220
20	4-OH	OCH_3	CH_2OH	–	>100	–	–

The biological activity data of 5,6-dihydropyrone analogues obtained from Hagen *et al*[4]. The biological activity was changed into -log (biological activity) to decrease the variance and to convert the data into free

energy change related values. The physico-chemical descriptors of the compounds obtained from substituent constants for correlation analysis in chemistry and biology developed by Hansch and Albert Leo, the indicator variables and -log (biological activity) were entered into excel worksheet. The QSAR model was developed with the help of statistical softwares[5]. Using multiple stepwise regression analysis, the correlation between biological activity and physico-chemical descriptors were performed to select the parameters with the minimum intercorrelation. The following statistical parameters were calculated *viz.*, correlation coefficient (r), squared correlation coefficient (r^2), F test values and standard deviation (s).

From the regression analysis, a number of equations correlating biological activity with physico-chemical descriptors were obtained. The best QSAR model predicting the biological activity with the physico-chemical descriptors is as under:

$-\log IC_{50} = 0.068\ (\pm\ 0.031)MR-0.729(\pm\ 0.968)F-0.322(\pm\ 0.488)\ R_2-1.477\ (\pm\ 0.359)$

$n = 17,\ r = 0.779,\ r^2 = 0.600,\ F = 6.724,\ S = 0.390$

The model revealed that molar refractivity (MR) contributes positively, whereas field effect (F) and presence of substituent at position R_2 contributes negatively to enzymatic activity ($-\log IC_{50}$). It was concluded that electronic descriptors are important for enzymatic and cellular toxicity of the pyrone derivatives.

Conclusion

The study led us to conclude that the binding pattern of the pyrone derivatives to the protease enzyme plays vital role in the inhibition of the enzyme activity. From the study the important properties of the substituent at particular positions of the pyrone nucleus that would lead to proper orientation of the compound at the binding pocket of the enzyme were explored. Utilization of this result in three dimensional QSAR analysis would be highly beneficial for the designing of newer pyrone analogues with maximal HIV protease inhibitory activity.

REFERENCES

1. S.F. Barre, J.B. Cherman, S. Charmet and L.G. Montagnier, *Science*, **220**, 868 (1983).
2. M. Papovic, M.G. Sargadharan, E. Read and R.C. Gallo, *Science*, **224**, 497 (1984).
3. www.skynet.ie.lnclairs/protease.html.
4. S.E. Hagen, J.V.N. Vara Prasad, F.E. Boyer, J.M. Domagala, E.L. Ellsworth, C. Gajda, W.H. Hamilton, L.J. Markoski, B.A. Steinbaugh, B.D. Tait, E.A. Lunney, P.J. Tummino, D. Ferguson, D. Hupe, C. Nouhan, S.J. Gracheck, J.M. Saunders and S. VanderRoest, *J. Med. Chem.*, **40**, 3707(1997).
5. H. Kubinyi, *Quant. Struct. Act. Relat.*, **13**, 285 (1994).

(*Received*: 4 January 2006; *Accepted*: 14 March 2007) AJC-5524