A QSAR STUDY UPON THYMINE DERIVATIVES WITH ANTI-HIV ACTIVITY

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ABSTRACT :

The basic goal in developing any chemotherapeutic agent is that it produces its desired effect without compromising host functions by unacceptable reverside effects. But, in viral infections the invader becomes a component of the host cell.

Herein we describe a QSAR study of a series of HEPT compunds, in which both the influence of substitution of the terminal hydroxy group (with and without 6-phenyl-6-thiopyridyl exchange) and the more extensive alteration of the N^1 side chain have been considered. We applied in this study the MTD method. and some other structural parameters, such as ClogP – the calculated octonal/water partition coefficients of the molecules under study.

KEYWORDS :

HIV, chemotherapic agents, HEPT, MTD method

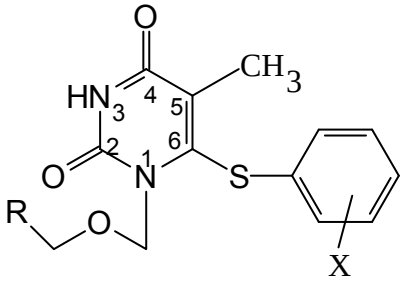
1. INTRODUCTION

Inhibition of reverse transcriptase (RT), the unique nucleic acid polymerizing enzyme – human immunodeficiency virus (HIV) – encoded polymerase which directs both RNA and DNA dependent DNA synthesis, preventing retrovirus replication, has proven to be one of the most effective ways to block the viral multiplication. There are several classes of compounds, which are specifically targeted at HIV-1 RT, from which the 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) derivative family has been extensively investigated [1].

2. METHODS

The biological activity for a small series of N^1 side chain modified analogues of HEPT, expressed as IC_{50}, is presented in Table 1.

Table 1. *Anti- HIV-1 Activity Data of Several HEPT Derivatives (IC_{50}) and calculated hydrophobicity (Clog P)*



compd	X	R	IC_{50}(μM)[a]	A[c]	Clog P
1.	CH	NH–C_6H_5	0.055	7.26	3.62
2.	N	NH–C_6H_5	0.160	6.80	2.52
3.	N	S–Py[b]	0.440	6.36	2.28
4.	CH	Br	0.760	6.12	2.80
5.*	CH	S–Py[b]	0.830	6.08	3.38
6.*	N	S–C_6H_5	1.010	6.00	3.38
7.*	CH	I	2.200	5.66	3.19
8.	CH	N(C_6H_5)$_2$	8.750	5.06	5.89
9.	CH	NHCO(CH_2)$_2$Cl	11.400	4.94	1.93
10.	CH	N(CH_2CN)$_2$	27.500	4.56	1.44
11.	CH	NH_2	31.000	4.51	1.44

*data points not used in deriving eq. (2).

[a]Effective concentration of compound required to achieve 50% inhibition of HIV-1 multiplication in CEM-SS infected cells

[b]Py = 2-pyridyl

[c]A =log1/C (C=IC_{50})

3. MTD METHOD [2]

The minimal steric difference, MTD, is a measure for steric misfit between the molecules of a series of bioactive substances and the binding site of the biological receptor, which is represented by the hypermolecule, **H**. The hypermolecule is the result of the approximate (non-hydrogen) atom per atom superposition of the molecules i, i=1,N, in the investigated series.

The vertices j, j=1,M of the hypermolecule correspond to the positions of these atoms. Thus, the hypermolecule **H** can be considered as a topological network. If molecule "i" occupies vertex "j" from **H**, x_{ij}=1, while x_{ij}=0, if the vertex is not occupied. The minimal steric difference MTD_i of molecule "i" with respect to the receptor is calculated according to the formula (1):

$$MTD_i = S + \sum \varepsilon_j x_{ij} \qquad (1)$$

with ε_j= –1, 0 or +1 for vertices attributed to the receptor cavity (beneficial), to the exterior (irrelevant) and to the receptor walls (detrimental), respectively; S is the total number of cavity vertices. Consequently, MTD_i is a measure of the steric misfit of the molecule "i" with respect to the receptor cavity and it is equal to the number of occupied wall vertices plus the number of unoccupied cavity vertices of **H** [3].

4. RESULTS AND DISCUSSIONS

The superposition procedure to construct the hypermolecule is based upon the maximal superposition of the compounds 2-11 upon the compound 1, which is the most active of this series. The entities to be superimposed are second or higher row atoms (S, Cl, Br, I).

The starting map for the MTD optimized procedure were obtained by inspection of vertices found preferentially in molecules with high and low inhibition activity, respectively. For all 11 compound from Table 1, it is:

$$S_t^o = \begin{cases} j(\varepsilon_j = -1): & 1-6 \\ j(\varepsilon_j = 0): & - \\ j(\varepsilon_j = +1): & 7-12 \end{cases} \qquad r = 0.695$$

The corresponding optimized receptor map, r being the correlation coefficient, and the correlation equation (2) are:

$$S_t^* = \begin{cases} j(\varepsilon_j = -1): & 4-7 \\ j(\varepsilon_j = 0): & 2,3,9,10 \\ j(\varepsilon_j = +1): & 1,8,11,12 \end{cases}$$

$$\hat{A} = 7.77(\pm 0.50) - 0{,}63(\pm 0.15)\mathrm{MTD} \qquad (2)$$
$$(n = 11, \quad r = 0.816)$$

***Table 2**. The results of the MTD method:*

i	j(x_{ij}=1)[a]	MTD_i* [b]	MTD_i* [c]
1.	1–6	2	3
2.	1–6	2	3
3.	1–6	2	3
4.	–	4	5
5.	1–6	2	–
6.	1–6	2	–
7.	–	4	–
8.	1–12	4	5
9.	1–4	4	5
10.	1,2,7,8	5	6
11.	–	4	5

[a]j – vertices occupied by molecule i in the hypermolecule **H**
[b]MTD – values corresponding to the S_t* optimized receptors map
[c]MTD – values corresponding to the S_p* optimized receptors map

For the smallest series, outliers are compounds 5-7 from Table 1 – the starting map S_p^o is:

$$S_p^o = \begin{cases} j(\varepsilon_j = -1): & 1-6 \\ j(\varepsilon_j = 0): & - \\ j(\varepsilon_j = +1): & 7-12 \end{cases} \qquad r = 0.749$$

The optimized receptor map S_p* and the corresponding correlation equation (3) A vs. MTD* are the following:

$$S_p^* = \begin{cases} j(\varepsilon_j = -1): \ 2,4-6,9 \\ j(\varepsilon_j = 0): \ 7,10 \\ j(\varepsilon_j = +1): \ 1,3,8,11,12 \end{cases}$$

$$\hat{A} = 9.15(\pm 0.80) - 0,79(\pm 0.18)MTD^* \quad (n = 8, \ r = 0.876) \qquad (3)$$

By using the ClogP values estimated by Hansch et al [4] and the MTD* values corresponding to the two optimized maps, the following correlational equations (4) and (5) have been obtained:

$$\hat{A}=4.49(\pm 1.64) + 1.54(\pm 0.74)\ Clog\ P - 0.20(\pm 0.1)(Clog\ P)^2 - 0.38(\pm 0.18)MTD^* \qquad (4)$$

$(n=11,\ r=0.891,\ s=0.49,\ F=9,\ p<0.008,\ q^2=0.706)$

$$\hat{A}=2.74(\pm 0.96) + 4.09(\pm 1.16)ClogP \qquad (5)$$

6. CONCLUSIONS

The obtained correlative results are good. However, the number of analyzed compounds is not big enough and their structural variation restricted. This hindered the performance of a detailed QSAR analysis, which would have allowed the obtaining of more accurate information upon the nature of the atomic groups in R.

The hydrophob character of those increases the anti-HIV activity by means of growing the degree of enzymatic inhibition of RT, acting upon the allosteric hydrophobic site (situated in the neighbourhood of the catalytic site of the enzyme) which imposes steric compulsions, revealed by our QSAR analysis with the MTD method.

The phenylic cycle, rigide and sufficiently hydrophil, is the best substituent for the studied series; the presence within the substrate R of some heteroatoms which decrease the hydrophobicity has a decreasing effect upon the biological activity.

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