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Original Article

Modelling of Anti-HIV-1 Activity of Piperidine-4-carboxamide CCR5 Antagonist: Role of Structural Manipulation

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ABSTRACT: Present study is aimed to understand the role of structural manipulation in modeling of anti-HIV-1 activity of Piperidine-4-Carboxamide CCR5 antagonists. For the purpose a set of 21 Piperidine-4-Carboxamide has been chosen. Study explores the role of various, structural features like size, substitution and steric properties in anti-HIV-1 activity of Piperidine-4-Carboxamide CCR5 antagonists derivatives. Multiple regression method is adopted to understand the role of structural manipulation in modeling the logIC_{50} activity. Statistics generated from the study shows that none of the parameter having statistical significant value of r but bi-parametric to tetra-parametric combinations produced the improved regression value.

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INTRODUCTION

The Greater the medicinal objective, the less likely it is for a new drug to be developed. Thus, the medicinal requirements affect the likelihood of success or failure in evolving new drugs. Now a day precise medicinal compounds to be prepared are generally suggested by the computational chemists and the consequently the attributes of the computational chemists will influence the outcome of evolving new drugs.

Recent advances of chemokine receptors functioning as HIV-1 have provided a novel strategy for controlling HIV-1 infection [1].

HIV-1 strains that cause the initial infection primarily utilize CC chemokine receptor 5 (CCR5) [2] and CCR5-using (R5) HIV-1 is isolated predominantly during the asymptomatic stage of the infection, which usually persists 5-10 years [3]. CCR5 belongs to the seven-transmembrane G protein-coupled receptor superfamily, and its natural ligands include the CC chemokines macrophage inflammatory protein (MIP)-1R, and MIP-1â], which have been reported to inhibit R5 HIV-1 infection in vitro [4].

Subsequent optimization identified a series of piperidine-4-carboxamide derivatives, exemplified low nanomolar affinity for CCR5 and exhibited good anti-HIV-1 activity [5].

The biological activity and the biological active sites of the receptors and the medicinal compounds are having the certain structural specifications, responsible for the development of molecule receptor complex and its stability.

The continuous development of structural and molecular descriptors those succeed to define the structural specification of molecules for biological activity with the help of statistical equations transformed the designing into powerful and widely used mathematical models for the prediction of biological activities or functions [6-11].

In the present work, efforts are made to signify the role of structural manipulation in series of piperidine-4-carboxamide derivatives using structure based topological, physicochemical parameters and the parameters accounted for the substitution effect for understanding their potential for CCR5 Antagonist (TAK-220) compounds.

Parent moiety of piperidine-4-carboxamide derivatives presented in Figure 1 and the derivatives are presented in Table 1.

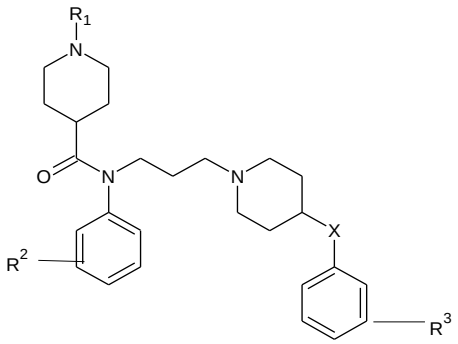

Figure 1: Parent structure of Piperidine-4-Carboxamide derivative

Table 1: Various substituent of piperidine-4-carboxamide investigated in the present study

Comp. No.	R_1	R2	X	R_3
1	Ms	3,4-diCl	CH_2	4-Ms
10	Ms	3,4-diCl	NHCO	4-F
11	Ms	3,4-diCl	CH_2	4-CN
12	Ms	3,4-diCl	CH_2	4-CO_2Me
13	Ms	3,4-diCl	CH_2	4-CO_2H
14	Ms	3,4-diCl	CH_2	4-$CONH_2$
15	Ms	3,4-diCl	CH_2	3-$CONH_2$
16	Ms	3,4-diCl	CH_2	2-$CONH_2$
17	Ms	3,4-diCl	CH_2	4-CONHMe
18	Ms	3,4-diCl	CH_2	4-CONH*t*-Bu
19	Ms	3,4-diCl	CH_2	4-$CONMe_2$
2	Ms	3,4-diCl	CH_2	4-F
20	Ac	3,4-diCl	CH_2	4-$CONH_2$
21	Ac	3-Cl,4-Me	CH_2	4-$CONH_2$
3	Ac	3,4-diCl	CH_2	4-F
4	Ac	H	CH_2	H
5	Ac	3,4-diCl	S	4-F
6	Ac	3,4-diCl	SO	4-F
7	Ac	3,4-diCl	SO_2	4-F
8	Ac	3,4-diCl	NH	4-F
9	Ms	3,4-diCl	$NHSO_2$	4-F

METHODOLOGY

In proposed study methodology will be adopted is based on aspect of Quantitative Structure Activity Relationship i.e, to develop mathematical model based on relation:

$$\phi = f(C)$$

where, ϕ = Biological activity; C = Structural descriptor/ physicochemical properties; C used in present work are topological parameters, physicochemical properties and other molecular features; f = Function of structure

Physicochemical properties used in present investigation are

1. Parachor (Pc)
2. Polarizability (Pol)

The Structural descriptor tested is

1. Wiener Index (W) [12]: Indicator parameters are also used along with indices and physicochemical properties to show the significance of substituents on various positions. Indicator parameters are the descriptors having value 1 or 0 to indicate the presence or absence of substituents at a specific position. In present investigation indicator parameter tested is
2. I_{MS} = Indicator parameter for Mesityl group at R_1 position in the parent moiety.

During proposed study methodology used is as follows:

In the very first step Molecule and its analogs must be selected with their experimental biological activity [13]. This extended to drawing the structures of studied compounds using suitable software [14-16] and generates the structure-based descriptors, physicochemical properties and molecular parameters.

In the second step structural descriptors physicochemical-properties and molecular descriptors will be correlated with the biological activity, to perform this Multiple linear regression (MLR) [17] method is used.

RESULTS AND DISCUSSION

Extracting numerical codes of the 3D structures is an important part of computation. The numeric codes in the form of independent variables are tested in regression analysis to predict biological activity. In the present study, two classes of structural descriptors have been tested. The descriptors tested are listed in Table 2.

The topological descriptors are purely structure-based descriptors, representing size, shape, branching, and connectivity in the molecule.

Physicochemical descriptors are representing physical and chemical behavior of the compound which in turn is a consequence of their 3-dimensional structure.

Table 2: Structural parameters tested in present study

Comp. No.	W	Pc	Pol	I_{MS}
1	6948	1311.6	65.45	1
10	6400	1234.4	61.66	1
11	5974	1241.3	61.93	1
12	6986	1297.5	64.52	1
13	6460	1254.1	62.61	1
14	6460	1266.8	63.44	1
15	6367	1266.8	63.44	1
16	6274	1266.8	63.44	1
17	6986	1305.4	65.28	1
18	8693	1421.9	70.79	1
19	7514	1343.5	67.21	1
2	5490	1201	60.16	0
20	6050	1232.4	61.87	0
21	6050	1233.5	61.84	0
3	5122	1166.5	58.33	0
4	4103	1084.9	54.45	0
5	5122	1178.9	59.89	0
6	5440	1199.5	60.23	0
7	5760	1206.1	60.21	0
8	5122	1154.7	58.35	0
9	6768	1268.8	63.27	0

*****W = Wiener Index; Pc = Parachore; Pol = Polarizability; I_{MS} = Indicator parameter for Mesityl group at R_1

Along with these two types of descriptors dummy parameters or Indicator parameters are also tested to find out the effect of structural manipulation on biological function of the molecule.

The successive mathematical models obtained from the step wise regression analysis are indicating that none of the structural parameter or indicator parameter played significant role alone in modeling of anti-HIV activity. The best univariate model obtained from the structural parameters is given below in the form of Eq (1).

$\log IC_{50}$ = 0.4297 (±0.2662) Ims + 0.6086 …..…… Eq (1)

N = 21, r = 0.3473 Se = 0.6092 F = 2.606

Equation 1 indicates the unfavorable presence of Mesityle group on R1 position i.e., the presence of Mesityle group on R1 position in the molecule reduces the biological function. As the regression coefficient of the model is less than 0.5 it may not be considered significant but can be use as guiding factor related to structural manipulation for anti-HIV activity of the compounds.

For the detailed illustration of relationship between structural manipulation and biological function of the compounds biparametric combination have been tested and it is found that the combination of Wiener index representing the size of the molecule and Parachore representing the inverse steric properties with expanded surface played the significant role in modeling of anti-HIV activity for Piperidine-4-carboxamide derivatives. It is worth mentioning here, the biparametric model does not contain Indicator parameter I_{MS}.

Model obtained from above parameters is presented as eq. 2.

$\log IC_{50}$ = 0.0028 (±0.00076) W - 0.0374 (±0.0104) Pc + 29.9982 ……. Eq (2)

N = 21, r= 0.6590, Se = 0.5020 F = 6.908

From the perusal of equation 2 it is observed that the Wiener index is having the direct relation with studied biological activity numerically and at the same time Parachore (expanded surface) showing the inverse relationship with the biological activity.

Direct relationship of Wiener index with biological activity indicate increase only in size due to any substitution or change in structure leads towards the reduction in the anti-HIV activity of Piperidine-4-carboxamide derivatives. From the same equation it is also informed that the increase in surface or expanded surface will favor the biological activity. i.e, any change, which increase in the value of Parachore and surface of the molecule leads towards the higher anti-HIV activity. Inverse relation of Parachore with biological activity also indicates, any substitution or change in molecular structure for increase in size with higher steric properties will favor the biological activity.

The statistics generated from equation 2 is significant but not adequate to explain the overall role of structural manipulation in anti-HIV activity of Piperidine-4-carboxamide derivatives. Thus, tri and tetravariate combinations have been tested and the models obtained are presented in eq. 3 and 4 respectively.

$\log IC_{50}$= 0.003 (±0.000595) W–0.447 (±0.0084) Pc + 0.8645 (±0.2417) Ims + 37.2417…… Eq (3)

N = 21 r = 0.8221, Se = 0.3910, F = 11.815

$\log IC_{50}$ = 0.0035(±0.00058) W – 0.0909(±0.0220) Pc + 0.8139(±0.3647) Pol + 0.9851(±0.2247) Ims + 40.87 ….Eq (4)

N = 21 r = 0.8676, Se 0.3520, F = 12.181

As we pass from equation 1 to 4 there is significant improvement in the value of correlation coefficient justify the addition of parameters. It is observed that the parameters added in step up process are leading towards the size and steric properties of the molecules studied. It is also indicated by the models that any structural manipulation increases the expanded surface will be favorable for the anti-HIV activity of the Piperidine-4-carboxamide derivatives.

Addition of parameter I_{MS} in eq. 2 lead towards the tremendous increase in the regression value, also indicate that the Mesityl substitution may increase the size of the molecule along with the expanded surface. Comparison of magnitude amongst the parameters also indicates the dominance of expanded surface over the size. Further addition of polarizability (Pol) parameter in the eq. 3 confirms the findings of model 3.

From the perusal of eq. 4, information can be drawn that, addition of polarizability parameter reduces the magnitude of Pc significantly in the model but having negligible effect on the parameter W and I_{MS}.

This change in magnitude of parameter indicates the nonlinear behavior of parameter Pc i.e., Increase in the expanded surface is favorable up to certain limit only for the studied biological activity. Equation also suggests higher polarizability will not favor the biological activity of the Piperidine-4-carboxamide derivatives as CCR5 antagonist.

Parametric interrelationship also indicates the presence of Mesityl group on the molecule will increase the value of Paracore but this increase is very irregular in pattern, i.e, this relationship may affect by the other factors also.

It is worthy to mention that as we pass from eq. 2 to 4 there is leaner change in magnitude of parameter Wiener index indicates the linear relationship between biological activity and size of the Piperidine-4-carboxamide derivatives.

Results obtained from eq. 4 are recorded in table 3 and graphically presented in figure 2.

Table 3: Experimental and predict $logIC_{50}$ value along with residue using Eq (4)

Comp. No	Obs. $logIC_{50}$	Calc. $logIC_{50}$	Residue
1	0.342	0.433	-0.091
10	2.863	2.431	0.432
11	0.230	0.519	-0.289
12	0.663	1.092	-0.429
13	1.820	1.625	0.195
14	0.949	1.146	-0.197
15	0.447	0.817	-0.370
16	1.079	0.489	0.590
17	0.708	0.992	-0.284
18	1.041	0.915	0.126
19	1.279	0.964	0.315
2	0.519	0.047	0.472
20	0.580	0.562	0.018
21	0.544	0.438	0.106
3	0.079	0.394	-0.315
4	1.204	1.055	0.148
5	0.230	0.537	-0.307
6	0.505	0.064	0.441
7	0.462	0.578	-0.116
8	1.301	1.483	-0.182
9	0.662	0.928	-0.266

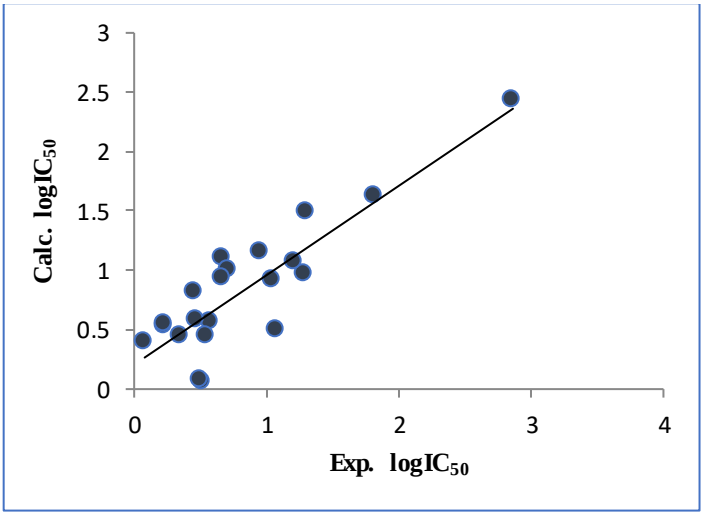

Figure 2: Graph obtained between experimental and calculate biological activity using equation 4

CONCLUSION

In the present work, effort is made to assess the role of structural manipulation on anti-HIV-1 activity of Piperidine-4-Carboxamide derivatives as CCR_5 antagonists.

As could be seen from the statistical plot presented, the optimum number of parameters for the correlation equation is four.

From the study conclusion can be drawn that increase in the size of the molecule due to any substitution or change may not favor the inhibition activity but increase leads toward the expanded surface area will be favorable for studied biological activity. Compounds having the higher value of parachore or substitution leads toward the high parachore can be consider as favorite for anti-HIV-1 activity of Piperidine-4-Carboxamide derivatives as CCR_5 antagonists. Conclusion also can be drawn that the higher value of polarizability is not favorable for the studied biological activity.

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