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Computational Modeling of Piperidine-4-Carboxamide Derivatives

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ABSTRACT

QSAR studies on Anti HIV-1 activity of Piperidine-4-Crboxamide Derivatives have been discussed. The topological, physicochemical, and hydrophobic parameters, indicator parameters were used. The predictive power of the model was examined using a CCR_5[a]log$IC_{50.}$

Keywords: QSAR, Anti HIV-1, Topological indices, physicochemical properties and logP.

INTRODUCTION

It is widely accepted that the primary etiological agent for the acquired immunodeficiency syndrome is the human immunodeficiency virus type1 (HIV-1)[1].studies on the molecular biology of HIV have identified its reverse transcriptase (RT) as one of the main targets for AIDS therapy. RT plays an essential role in the early steps of the replication cycle of retroviruses. RT catalyses the transcription of the HIV-encoded single-stranded RNA into double- stranded DNA[2].

The NNRTI, as opposed to the nucleoside analogues, constitute a number of different, structurally unrelated, classes of compounds that are targeted at a non- substrate binding site of this enzyme [3,4].

One class of compounds that has been identified as a potential therapeutic agent is the non- nucleotide reverse transcriptase inhibitor denoted as Piperidine-4-Carboxamide[5]. These compounds act by a mechanism distinct that of nucleoside analogs and its inhibits reverse transcription [6, 7]. Piperidine-4-Carboxamide specifically inhibits HIV-1 replication at nanomolar concentration [8, 9]. It represents a different class of inhibitors in that it inhibits HIV-1 reverse transcriptase alone. However Piperidine-4-Carboxamide is dependent on the type of primer used. Several analogs of the parent Piperidine-4-Carboxamide as Halogenated in the aromatic ring have been studied and demonstrated anti-HIV activity at low concentration [10, 11].

Many structure based techniques of drug discovery and development have involved in the past 20 years during the search for therapeutically useful agents in the treatment of acquired immunodeficiency syndrome (AIDS).

In the present work, a quantitative structure activity study has been performed to develop mathematical relationship between structural descriptors and biological activity to obtain more information about the structural requirement underlying the inhibition of NNRT. The graph topological indices and physicochemical properties used for investigate various structure activity relationships a series of derivatives of Piperidine-4-Carboxamide use for QSAR studies. These might be useful for the development of further drugs, active against the HIV-1 reverse transcriptase activity. For QSAR modeling we have used maximum R^2 method and followed stepwise regression analysis [10].

EXPERIMENT AND METHODOLOGY

Quantitative structure-activity relationships (QSAR) have been established for set of 21 analogues of Piperidine-4-Carboxamide (fig.1) a potent inhibitor of the HIV-1 reverse transcriptase (RT). The activity of these compounds was adopted from the literature .Table 1.

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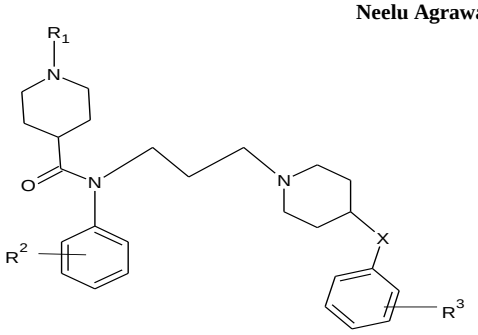


Fig.1 Parent structure of Piperidine-4-carboxamide Derivatives used in present study

Topological, physicochemical, and hydrophobic parameters were used as Three separate descriptors Topological descriptors such as Winer index (w) [12], Randic connectivity index (χ) [13],Balaban J index (J) [14], Szeged index (Sz) [15], Shultz molecular topological index (MTI) [16]and Electrotopological index (S) [17] were used to tested –momo, -di, -tri, -tetra variate combinations. Similarly in case of physicochemical properties Molar refractivity (MR), Molar volume (MV), Parachor (Pc), Index of refraction (IR), Surface tension (ST), Density (D) and Polarisability (Pol) were tested in various combinations. Since logP is an important property effecting biological activities, therefore, it is tested separately from other physicochemical properties. All the physicochemical properties are calculated using ACD chemsketch software [18]. All the regression is carried out using maximum r^2 method [19]. Step wise regression has been performed for obtaining the best model. Molecular modeling is using Hyperchem-lite [20].

Table 1. Biological activity and different substituent of Piperidine-4-carboxamide

Compound	R^1	R^2	X	R^3	$CCR_5{}^a logIC_{50}$(nm)
1	Ms	3,4-diCl	CH_2	4-MS	0.342
2	Ms	3,4-diCl	CH_2	4-F	0.519
3	Ac	3,4-diCl	CH_2	4-F	0.079
4	Ac	H	CH_2	H	1.204
5	Ac	3,4-diCl	S	4-F	0.23
6	Ac	3,4-diCl	SO	4-F	0.505
7	Ac	3,4-diCl	SO_2	4-F	0.462
8	Ac	3,4-diCl	NH	4-F	1.301
9	Ms	3,4-diCl	$NHSO_2$	4-F	0.662
10	Ms	3,4-diCl	NHCO	4-F	2.863
11	Ms	3,4-diCl	CH_2	4-CN	0.23
12	Ms	3,4-diCl	CH_2	4-CO_2Me	0.663
13	Ms	3,4-diCl	CH_2	4-CO_2H	1.82
14	Ms	3,4-diCl	CH_2	4-$CONH_2$	0.949
15	Ms	3,4-diCl	CH_2	3- $CONH_2$	0.447
16	Ms	3,4-diCl	CH_2	2- $CONH_2$	1.079
17	Ms	3,4-diCl	CH_2	4-CONHMe	0.708
18	Ms	3,4-diCl	CH_2	4-CONHt-Bu	1.041
19	Ms	3,4-diCl	CH_2	4-$CONMe_2$	1.279
20	Ac	3,4-diCl	CH_2	4- $CONH_2$	0.58
21	Ac	3-Cl,4-Me	CH_2	4- $CONH_2$	0.544

a Inhibition of 125I-labeled RANTES binding to CCR5-expressing CHO cells.

RESULT AND DISCUSSION

As mentioned in introduction QSAR studies on set of Piperidine-4-Carboxamide derivative containing 21 compounds is performed. The topological indices, physicochemical properties and $CCR_5 logIC_{50}$.Topological descriptors and physicochemical properties were tested in various combinations using MLR. Shown in Table 2. Table 3.Table 4. The best correlation obtained using topological indices 0.6241, this is significant result, but this result is not consider as the very efficient for the prediction purpose, but however it is worthy for the screening of W and J from the other topological indices. The prediction of Biological activity i.e., inhibition of 125I-labeled RANTES binding to Chinese hamster ovary (CHO) cells expressing human CCR5 on their surface is calculated using mathematical model obtained from topological indices shown in Table 5. The correlation between experimental and calculated activity is shown in **Figure 3.**

Table 2: Topological indices and indicator parameter.

Compound	χ^0	χ^1	W	J	Ims	Ix
1	29.7858	43.7601	6948	1.2179	1	1
2	27.2858	40.7723	5490	1.2411	0	1
3	26.3632	39.7774	5122	1.2317	0	1
4	23.7525	36.8084	4103	1.2035	0	1
5	26.3632	39.7774	5122	1.2317	0	0
6	27.2334	40.7676	5440	1.2495	0	0
7	28.1561	41.7610	5760	1.2695	0	0
8	26.3632	39.7774	5122	1.2317	0	0
9	29.7858	43.7585	6768	1.2467	0	0
10	28.8632	42.7647	6400	1.2304	1	0
11	27.9929	41.7707	5974	1.2293	1	1
12	29.5703	43.7634	6986	1.2127	1	1
13	28.8632	42.7647	6460	1.2218	1	1
14	28.8632	42.7647	6460	1.2218	1	1
15	28.8632	42.7647	6367	1.2372	1	1
16	28.8632	42.7645	6274	1.2536	1	1
17	29.57034	43.7634	6986	1.2127	1	1
18	32.0703	46.7556	8693	1.1920	1	1
19	30.4405	44.7578	7514	1.2072	1	1
20	27.9405	41.7695	6050	1.2124	0	1
21	27.9405	41.7695	6050	1.2124	0	1

Where,

χ^0 = Zero order connectivity index, χ^1 = First order connectivity index, W = Wiener index

J = Balaban branching index, Ims = Indicator parameter for Mesityl group at R_1

Ix = Indicator parameter for $–CH_2-$ group at X.

Table 3: Physicochemical properties tested in present investigation

Compound	XlogP	SlogP	vdW	Hf	IP
1	3.312	5.606	753.711	-69.287	9.073
2	4.19	5.912	691.538	-59.861	9.050
3	5.633	6.068	685.364	-32.062	9.017
4	4.293	4.622	621.122	-3.4450	8.900
5	5.45	6.370	688.363	-3.4450	8.900
6	3.702	5.601	692.530	-47.485	8.621

7	4.356	5.482	696.791	-102.783	9.020
8	4.863	5.690	680.170	-22.482	8.238
9	1.539	4.830	733.510	-91.728	9.080
10	3.03	4.851	708.524	-72.977	9.117
11	3.807	5.644	720.654	24.785	9.065
12	3.997	5.559	762.188	-90.701	9.025
13	3.66	5.471	734.311	-95.481	9.021
14	2.944	4.871	739.883	-45.476	9.019
15	2.944	4.871	739.747	-43.230	9.051
16	2.944	4.871	732.690	-33.466	9.069
17	3.434	5.132	770.342	-48.218	9.019
18	4.745	6.301	813.401	-47.228	9.006
19	3.573	5.474	783.199	-53.687	9.020
20	4.387	5.028	721.125	-45.329	9.007
21	4.049	4.683	725.205	-46.627	8.928

Where,
XlogP & SlogP = *XlogP* (by Kellog method) and the *SlogP* (by Audry method) most hydrophobic hydrophilic distance descriptors, vdW = Vander Waal Surface area,
Hf = Heat of Formation, IP = Ionization Potential

Table 4: Physicochemical Properties.

Compound	DM	MR	MV	Pc	IR	ST	D	POL
1	2.454	165.1	464.9	1311.6	1.628	63.3	1.38	65.45
2	3.900	151.77	434.9	1201.0	1.614	58.1	1.34	60.16
3	3.753	147.14	438.8	1166.5	1.585	49.9	1.249	58.33
4	2.909	137.35	410.7	1084.9	1.583	48.6	1.123	54.45
5	4.244	151.08	426.6	1178.9	1.626	58.2	1.32	59.89
6	4.967	151.94	422.7	1199.5	1.637	64.7	1.37	60.23
7	4.039	151.89	447.8	1206.1	1.593	52.6	1.336	60.21
8	4.164	147.2	425.4	1154.7	1.608	54.2	1.291	58.35
9	2.807	159.61	445.0	1268.8	1.636	66.0	1.45	63.27
10	3.257	155.54	439.1	1234.4	1.626	62.4	1.39	61.66
11	4.238	156.23	439.6	1241.3	1.628	63.5	1.34	61.93
12	3.267	162.77	464.9	1297.5	1.617	60.6	1.34	64.52
13	3.375	157.93	440.1	1254.1	1.636	65.9	1.38	62.61
14	3.543	160.02	446.3	1266.8	1.636	64.8	1.36	63.44
15	3.394	160.02	446.3	1266.8	1.636	64.8	1.36	63.44

16	3.106	160.02	446.3	1266.8	1.636	64.8	1.36	63.44
17	3.445	164.68	466.3	1305.4	1.624	61.3	1.33	65.28
18	4.579	178.58	514.9	1421.9	1.61	58.1	1.29	70.79
19	3.791	169.54	481.2	1343.5	1.622	60.7	1.32	67.21
20	2.545	156.07	453.3	1232.4	1.604	54.6	1.265	61.87
21	3.098	156	457.6	1233.5	1.597	52.7	1.208	61.84

Where,
DM = Total Dipole moment, MR = Molar refractivity, MV = Molar Volume, Pc = Parachor
IR = Index of refraction, ST = Surface Tension, D = Density, Pol = Polarizability

The univariate correlateness can be observed at the glance by considering correlation matrix, the correlation matrix implies that none of the topological indices shows significant correlation with CCR_5logIC_{50} (inhibitory action of the piperidine-4-carboxamide derivatives). The highest correlatedness has been shown by an indicator parameter Ims (possessing value = 1 if mesityl group at R_1 and zero if absent). With the perusal of correlation matrix, Ims has been considered in a univariate model, **Eq (1)** which coincidently not a topological descriptor. All other topological descriptors have been tested with the Ims to obtain bivariate, trivarate and tetravariate model and the tested combinations are shown in correlation table**.** On testing pentavariate model show no significant improvement in the predictive ability, also as per rule of five, i.e, one parameter on the set of 5 data set the regression analysis is restricted up to tetravariate combinations. The successive mathematical models obtained from the step wise regression analysis is given below in the form of Eq (1) to Eq (4) with their statistical parameters.

Univariate model

CCR_5logIC_{50} = 0.4297 (±0.2662) Ims + 0.6086 **Eq (1)**

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

Bivariate model

CCR_5logIC_{50} = 0.6627 (±0.2816) Ims - 0.5696 (±0.3113) Ix + 0.8934 **Eq (2)**

N = 21, r= 0.5084, Se = 0.5747 F = 3.138

Trivariate model

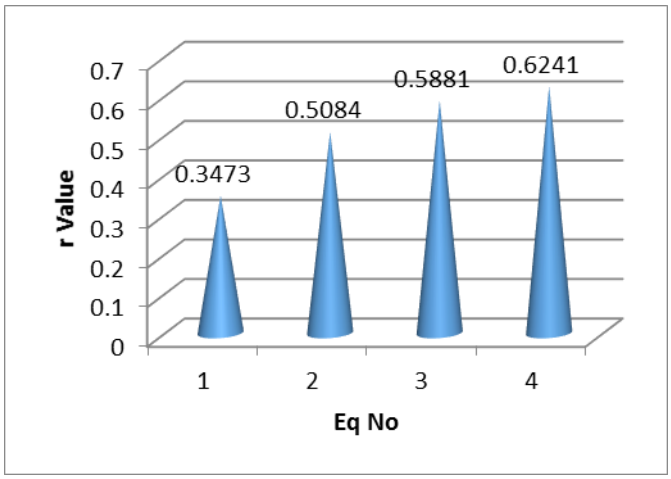
CCR_5logIC_{50} = 0.6287 (±0.2731) Ims - 0.8295 (±0.3468) Ix -12.1467 (±8.0609) J + 16.0014 **Eq (3)**

N = 21, r = 0.5881, Se = 0.555 F = 2.996

Tetravariate model

CCR_5logIC_{50} = 0.8815 (±0.3603) Ims - 0.9007 (±0.3517) Ix -14.749 (±8.3872) J – 0.00019213 (0.0001795) W + 20.3031 **Eq (4)**

N = 21, r = 0.6241, Se = 0.5531 F = 2.553



The relative raise in the r value can be easily observed by graph **Figure 2.**

Table 5. : Experimental and predicted biological activity (Using Eq (4) of topological indices) and residual value i.e., experimental – calculated activity of Piperidine-4-carboxamide Derivative.

Compound	Experimental CCR_5logIC_{50}	Calculated CCR_5logIC_{50}	Residual
1	0.342	0.985	-0.6428
2	0.519	0.044	0.4748
3	0.079	0.248	-0.1686
4	1.204	0.856	0.3476
5	0.23	1.148	-0.9183
6	0.505	0.822	-0.3167
7	0.462	0.465	-0.0033
8	1.301	1.163	0.1379
9	0.662	0.611	0.0512
10	2.863	1.814	1.0492
11	0.23	1.01	-0.7797
12	0.663	1.051	-0.3883
13	1.82	1.02	0.8004
14	0.949	1.02	-0.0706
15	0.447	0.816	-0.3692
16	1.079	0.583	0.4956
17	0.708	1.051	-0.3433
18	1.041	1.033	0.008
19	1.279	1.038	0.2407
20	0.58	0.364	0.2157
21	0.544	0.364	0.1797

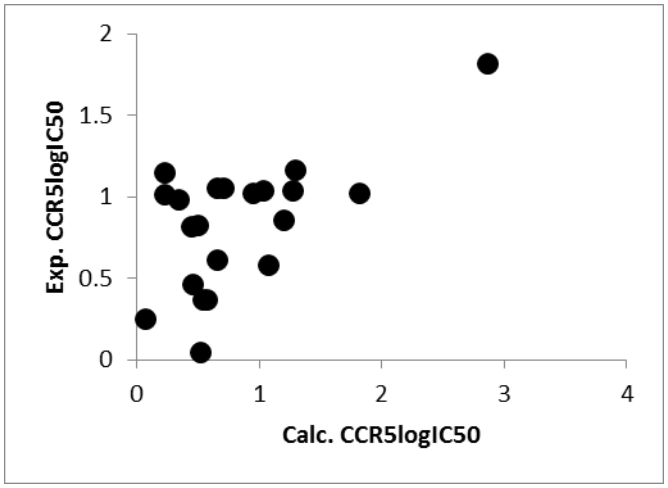


Figure 3. Graph between Experimental and Calculate biological activity using Eq (4).

The QSAR model in the form of Eq (4) indicate that Wiener index (W) and Balaban branching index (J), is inversely related to the value of CCR_5logIC_{50} i.e., with increase in the value of these indices , value of CCR_5logIC_{50} decreases, it revels that 50% inhibition takes place at lower concentration, which means increases inhibition activity. This fact favors high value of W and J for the compounds under consideration. High W and J leads to the compounds towards larger size and more branching. Similarly negative regression coefficient of Ix also, shows that the presence of –CH2- at X shows inverse relation with the value of CCR_5logIC_{50}, i.e., if –CH2-is present value of CCR_5logIC_{50} decreases, hence improved inhibition activity.

The only parameter with positive regression coefficient is Ims, this indicate that Ims is directly proportional to the value of CCR_5logIC_{50}, with the presence of mesityl group , value of CCR_5logIC_{50} increases, and increased value means higher concentration is needed for 50% inhibition, which concludes reduced activity. Therefore mesityl group is not favorable group.

CONCLUSION

On the basis of the above discussion we can draw following conclusion:

1. The present set of Piperidine-4-carboxamide Derivatives preference among the topological indices is: J > Ix > Ims > W.
2. For modeling chemokine receptors (CCR_5logIC_{50}) of the present set of compounds. The present of –CH2- at X shows inverse relation with the value of CCR_5logIC_{50}, i.e., if –CH2-is present value of CCR_5logIC_{50} decreases, hence improved inhibition activity.
3. High SlogP and D value seem to be favorable for the biological activity.

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