International Journal of Chemistry and Pharmaceutical Sciences

Journal Home Page: www.pharmaresearchlibrary.com/ijcps

Research Article **Open Access**

Quantum Molecular Modeling of Piperdine-4-Carboxamide Derivative CCR5 Antagonist (TAK-220) With Anti-HIV-1 Activity

Neelu Agrawal*[1], Parvinder Khanuja[2]

[1]*Department of Chemistry, M.L.C. Govt. G.P.G. College, Khandwa, M.P, India*
[2]*Department of Chemistry, S.N.P.G. College, Khandwa, M.P, India*

A B S T R A C T

QSAR and SAR studies on the Piperidine-4-Crboxamide Derivatives as non- nucleotide reverse transcriptase inhibitor of HIV-1 using the topological, physicochemical, and hydrophobic parameters, indicator parameters along with the quantum parameters. Application of multiple linear regression analysis indicated that a combination of different molecular descriptors and the indicator parameters yielded a statistically significant model for the prediction of activity, $CCR_5{}^{a}logIC_{50}$. The final selection of a potential Piperidine-4-Carboxamide Derivatives as non- nucleotide reverse transcriptase inhibitor of HIV-1 is made by the quantum molecular modeling.

Keywords: QSAR, Anti HIV-1, Topological indices, physicochemical properties and quantum descriptors and $logIC_{50}$.

A R T I C L E I N F O

CONTENTS

Article History: Received 18 August 2016, **Accepted** 21 September 2016, **Available Online** 27 October 2016

***Corresponding Author**
Neelu Agrawal
Department of Chemistry,
M.L.C. Govt. G.P.G. College,
Khandwa, M.P, India
Manuscript ID: IJCPS3119

PAPER-QR CODE

Citation: Neelu Agrawal. Quantum Molecular Modeling of Piperdine-4-Carboxamide Derivative CCR5 Antagonist (TAK-220) With Anti-HIV-1 Activity. *Int. J. Chem, Pharm, Sci.*, 2016, 4(10): 506-511.

Copyright© 2016 Neelu Agrawal. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Despite worldwide efforts to prevent the spread of human immunodeficiency virus type 1 (HIV-1), the number of HIV-1-infected people still continues to rise.[1]Recent advances of chemokine receptors functioning as HIV-1 co-receptors have provided a novel strategy for controlling HIV-1 infection.[2] HIV-1 strains that cause the initial

infection primarily utilize CC chemokine receptor 5 (CCR5),[3] and CCR5-using (R5) HIV-1 is isolated predominantly during the asymptomatic stage of the infection, which usually persists for 5-10 years.[4] CCR5 belongs to the seven-transmembrane G protein-coupled receptor super family and its natural ligands include the CC chemokines [regulated on activation, normal T cell expressed, secreted (RANTES), macrophage inflammatory protein (MIP)-1R, and MIP-1â], which have been reported to inhibit R5 HIV-1 infection in vitro.[5] Subsequent optimization identified a series of piperidine-4-carboxamide derivatives, exemplified low nanomolar affinity for CCR5 and exhibited good anti-HIV-1 activity.[6] In vitro metabolic stability studies in human hepatic microsomes, however, showed these compounds to be rapidly metabolized.[7]

2. Materials and Methods

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.

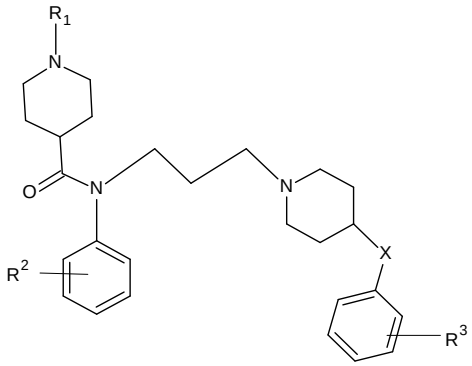

Figure 1: Parent structure of Piperidine-4-carboxamide Derivatives used in present study

Quantum Descriptors

In this category following descriptors were tested, these descriptors represents different electronic environment of the compound.

Total energy: The total energy serves to represents the chemical reactivity of the compounds.

Binding Energy: It is used as a measure of electronic interaction between drug and receptor

HOMO (Highest occupied Molecular Orbital) & LUMO (Lowest Unoccupied Molecular Orbital):

Energies associated with the highest occupied molecular orbital (EHOMO), and lowest unoccupied molecular orbital (ELUMO) are often good candidates for 2-dimensional descriptors. The HOMO energy is related to the ionization potential and is a measure of the molecule's tendency to be attacked by electrophiles. Correspondingly, the LUMO energy is related to the electron affinity and is a measure of a molecule's tendency to be attacked by nucleophiles[8, 9]

Dipole Moment:

The polarity is represented by the dipole moment. Polaris ability is a tensor relating the induced dipole moment to the applied electric field strength.

X, Y, Z coordinate of N atom:

Represents the electron density in all the 3 dimension of the molecule, but here Nitrogen atom has been selected , because it is an atom where regular substitution are observed.

Net charge and Electron density of few selective atoms.

Electron densities and net Charges on atoms are considered as non directional reactivity indices.

3. Results and Discussion

As mentioned in introduction QSAR studies on set of Piperidine-4-Carboxamide derivative containing 21 compounds is performed. The Quantum Descriptors tested in present study has been given in **Table 2 a, b & c.** The QSAR analysis using stepwise multiple linear regression method is also performed separately with Quantum descriptors, in a same manner as with topological descriptors and physicochemical descriptors. Here quantum descriptors are used as independent variable to predict the biological activity (dependent variable).

The corrlation matrix is shown in the form of **Table 3** there are two descriptors showing approximetely same correlation with biological activity. Therefore while testing bivariate combination, both the descriptors are examine with the second descriptor, or in words, in first step of screening two descriptrs are screened. These are Ims and EDN (Electron density at Nitrogen of R_1) with correlation value 0.34727 and -0.36306 respectively. The relative raise in the r value can be easily observed by demonstrating the graph below as **Figure 2.** It is clearly observed from the model obtained from quantum descriptors that EDN produces no significant result in further steps of regression analysis, therefore screened out from the regression analysis, and finally no appear in the final mathematical model.

The best correlation obtained using Quantum descriptors is 0.7101, this result is a significant result, and the model with such result may consider as the an efficient model for the prediction purpose, also it is worthy for the screening of HOMO and EDC4 from the other Quantum descriptors. These two descriptors are not seems as an important descriptor initially in correlation matrix, but both the descriptors are comeout as an operational descriptors.

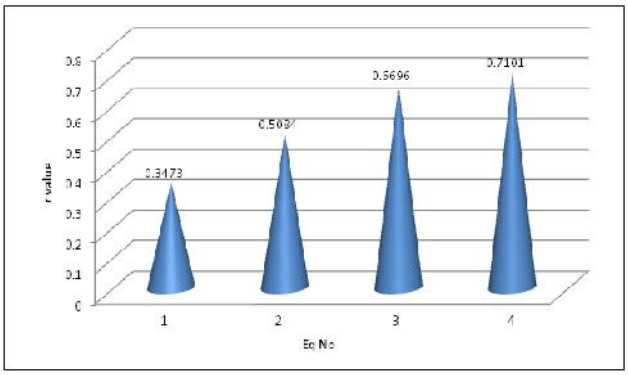

Figure 2 : Relative raise in the value of "r" from Eq (1) to Eq (4)

By the persual of Eq (4) Ims, Ix, HOMO and EDC4 are selected as a predictive descriptors among the physicochemical descriptors. 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 or predicted using mathematical model obtained from quantum descriptors and present in **Table 4.**The correlation between experimental and calculated activity is present in **Figure 3**

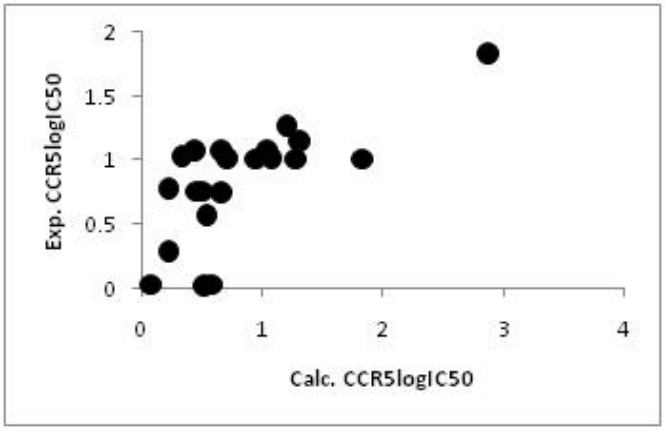

Figure 3: Graph between Experimental and Calculate biological activity using Eq (4)

4. Conclusion

The negative coefficient of Ix indicate that presence of –CH2- group decreases value of biological activity in a quantitative manner, i.e., presence of –CH2- is favorable. On the other hand positive coefficient of Ims, leads to the increase in the value of biological activity in a quantitative aspects, i.e., presence of mesityl group in unfavorable. The positive coefficient of HOMO shows that the value of **CCR_5logIC_{50}** increases with the increase in the value of HOMO,higher value of CCR5logIC50 is unfavorable. Therefore molecule should have such structure which possesses lower value of HOMO. Similarly The positive coefficient of EDC4 shows that the value of CCR_5logIC_{50} increases with the increase in the value of EDC4 (Electron density at 4^{th} Carbon), higher value of CCR_5logIC_{50} is unfavorable. **HOMO > EDC4 > Ims > Ix.** The QSAR model in the form of Eq (4) is the model obtained from Quantum parameters, it contains HOMO and EDC4 with the positive coefficient, and it means both the parameters are directly proportional to the value of CCR_5logIC_{50}. That means higher value of HOMO and EDC4 raise the value of CCR_5logIC_{50}, which implies that the higher concentration is needed for 50% inhibition activity. Therefore substitution which lower the energy of HOMO and Electron density at C4 is need to substitute in the compound to make is more biologically active.

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.

Table 2a: The Quantum Descriptors tested in present study

Compound	TE	BE	HOMO	LUMO	DM	Nx	Ny	Nz
1	2425.7	2806.6	-0.218	-0.14	7.31	-8.70	0.805	-0.008
2	2170.4	2523.8	-0.219	-0.14	8.50	-8.18	1.59	0.19
3	2042.0	2372.9	-0.218	-0.13	11.45	-7.94	1.27	0.16

4	1788.7	2061.8	-0.218	-0.04	5.82	-7.49	0.36	0.15
5	2025.9	2360.0	-0.216	-0.13	16.80	-8.03	1.30	0.14
6	2130.5	2482.7	-0.218	-0.13	17.98	-8.67	1.33	0.18
7	2241.8	2612.1	-0.218	-0.14	15.88	-7.31	-1.45	-3.02
8	2070.3	2405.4	-0.183	-0.13	10.94	-7.78	-0.41	0.57
9	2542.7	2947.4	-0.219	-0.17	10.47	-5.57	2.63	0.19
10	2383.2	2765.2	-0.216	-0.14	13.47	-7.44	0.88	0.08
11	2371.2	2714.4	-0.122	-0.11	26.28	-5.70	0.89	-1.1E-07
12	2381.2	2757.5	-0.219	-0.14	5.67	-9.60	1.50	-0.006
13	2300.2	2669.1	-0.220	-0.14	5.99	-9.01	1.48	-0.18
14	2300.2	2663.5	-0.220	-0.14	3.07	-9.06	1.48	-0.08
15	2305.7	2668.2	-0.219	-0.14	6.51	-8.61	1.60	-0.05
16	2344.5	2707.0	-0.219	-0.14	11.22	-7.76	1.59	-0.06
17	2379.3	2749.2	-0.219	-0.14	2.85	-9.67	1.57	0.04
18	2471.8	2849.1	-0.219	-0.14	3.80	-9.87	1.47	0.01
19	2471.8	2849.1	-0.220	-0.14	3.80	-9.68	1.53	-0.04
20	2168.1	2508.0	-0.218	-0.14	7.65	-9.02	1.19	-0.12
21	2176.6	2508.5	-0.213	-0.12	7.29	-9.01	1.04	-0.12

Where, TE = Total Energy, BE = Binding energy, HOMO = Energy of higest occupied molecular orbital LUMO = Energy of lowest unoccupied molecular orbital, DM = Dipole moment in ab initio molecular field, Nx = energy at x coordinate of N atom, Ny = energy at y coordinate of N atom, Nz = energy at z coordinate of N atom

Table 2b: Quantum Descriptors (Net charges)

Compound	**NCN**	**NCC3**	**NCC4**	**NCCX**	**NCC`X**	**NCCR3**
1	0.10	0.24	0.21	0.16	0.14	0.10
2	0.10	0.24	0.21	0.16	0.04	0.05
3	0.02	0.24	0.21	0.16	0.04	0.05
4	2.32	0.01	2.18	0.16	0.08	2.09
5	0.02	0.24	0.21	0.17	5.52	-0.03
6	0.02	0.24	0.21	0.18	0.02	-0.04
7	0.02	0.24	0.21	0.06	0.09	-0.03
8	0.02	0.24	0.21	0.15	0.18	-0.04
9	0.04	0.24	0.21	0.27	0.09	-0.03
10	0.11	0.24	0.21	0.15	0.07	-0.05
11	-0.28	0.24	0.21	0.28	0.02	0.11
12	0.11	0.24	0.21	0.11	3.96	3.23
13	0.11	0.24	0.21	0.10	3.47	0.02
14	0.11	0.24	0.21	0.10	0.03	0.03
15	0.10	0.24	0.21	0.10	0.01	0.02
16	0.11	0.24	0.21	0.097	0.03	0.03
17	0.10	0.24	0.21	0.10	0.02	0.03
18	0.10	0.24	0.21	0.09	0.03	0.02
19	0.10	0.24	0.21	0.11	0.02	0.03
20	0.028	0.24	0.21	0.11	0.02	0.03
21	0.031	0.17	0.12	0.11	0.02	0.03

Where, NCN = Net charge at Nitrogen of R_1 NCC3 = Net charge of C_3, NCC4 = Net charge on C_4, NCCX = Net charge on Carbon left to –X-, NCC`X = Net charge on Carbon right to –X-,
NCCR3 = Net charge on Carbon of R_3

Table 2c: Quantum Descriptors (Electron Density)

Compound	EDN	EDC3	EDC4	EDCX	EDC`X	EDCR3
1	4.89	3.76	3.79	3.84	3.86	3.90
2	4.89	3.76	3.79	3.84	3.96	4.05
3	4.98	3.76	3.79	3.84	3.96	4.05
4	4.98	3.98	4.02	3.84	3.92	3.98

5	4.98	3.76	3.79	3.84	3.96	4.05
6	4.97	3.76	3.79	3.82	3.98	4.04
7	4.97	3.76	3.79	3.94	3.91	4.04
8	4.97	3.76	3.79	3.84	3.82	4.05
9	4.95	3.76	3.79	3.73	3.90	4.03
10	4.89	3.76	3.80	3.85	3.99	4.06
11	5.28	3.96	3.45	3.72	3.97	3.89
12	4.89	3.76	3.80	3.89	3.96	3.97
13	4.89	3.76	3.79	3.90	3.97	3.98
14	4.89	3.76	3.79	3.90	3.97	3.97
15	4.90	3.76	3.80	3.90	3.98	3.97
16	4.89	3.76	3.79	3.90	3.97	3.97
17	4.89	3.76	3.79	3.90	3.97	3.97
18	4.90	3.76	3.80	3.90	3.97	3.97
19	4.89	3.76	3.79	3.89	3.97	3.97
20	4.97	3.76	3.79	3.89	3.97	3.97
21	4.97	3.83	3.88	3.89	3.97	3.48

Where, EDN = Electron Density on Nitrogen of R_1, EDC3 = Electron Density on C_3,EDC4 = Electron Density on C_4,EDCX = Electron Density on Carbon left to –X-,EDC`X = Electron Density on Carbon right to –X-,EDCR3 = Electron Density on Carbon of R_3

Table 3: Correlation matrix of Quantum descriptors with biological activity

	CCR_5logIC_{50}	**TE**	**BE**	**HOMO**	**LUMO**	**IMS**	**IX**	**NCN**
CCR_5logIC_{50}	1.000							
TE	.160	1.000						
BE	.163	.998	1.000					
HOMO	- .152	.022	-.005	1.000				
LUMO	.064	- .634	-.665	- .222	1.000			
IMS	.347	.673	.656	.090	- .114	1.000		
IX	- .174	.103	.070	- .008	.296	.452	1.000	
NCN	.196	- .561	-.576	- .215	.826	- .199	.155	1.000
NCC3	- .097	.606	.629	.064	-.888	.298	- .180	- .934
NCC4	.138	- .586	-.606	- .062	.874	- .223	.134	.984
EDN	- .363	- .198	-.225	.885	.331	-.210	- .080	- .076
EDC3	- .073	- .376	-.416	.587	.848	-.086	.236	.586
EDC4	.236	- .432	-.421	- .779	.304	-.322	- .004	.670
EDCX	.187	- .013	-.006	- .591	- .037	.231	.275	.025
EDC`X	.094	.136	.127	- .130	- .000	.317	.335	- .147
	NCC3	NCC4	EDN	EDC3	EDC4	EDCX	EDC`X	
NCC3	1.000	1.000						
NCC4	-.937	.090						
EDN	-.112	.694	1.000					
EDC3	-.732	.546	.692	1.000				
EDC4	-.606	- .088	- .647	- .096	1.000			
EDCX	.042	- .088	- .637	- .431	.452	1.000		
EDC`X	.114	- .158	- .033	- .013	- .133	.223	1.000	

Table 4: Experimental and predicted biological activity

Compound	**Experimental CCR_5logIC_{50}**	**Calculated CCR_5logIC_{50}**	**Residual**
1	0.342	1.03	-0.6876
2	0.519	0.014	0.5053
3	0.079	0.025	0.0539
4	1.204	1.268	-0.0639
5	0.23	0.778	-0.5483
6	0.505	0.756	-0.2506

7	0.462	0.756	-0.2936
8	1.301	1.152	0.1486
9	0.662	0.744	-0.0823
10	2.863	1.837	1.0262
11	0.23	0.281	-0.0508
12	0.663	1.072	-0.4093
13	1.82	1.007	0.8131
14	0.949	1.007	-0.0579
15	0.447	1.072	-0.6253
16	1.079	1.018	0.0608
17	0.708	1.018	-0.3102
18	1.041	1.072	-0.0313
19	1.279	1.007	0.2721
20	0.58	0.025	0.5549
21	0.544	0.568	-0.0241

Univariate model

There are two univariate model found with approximately results, therefore given in the form of Eq (1a) and (1b)

$CCR_5 logIC_{50}$ = 0.4297 (±0.2662) Ims + 0.6086 **Eq (1a)**

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

$CCR_5 logIC_{50}$ = -2.6514 (±1.5613) EDN + 0.5053 **Eq (1b)**

N = 21, r = -0.363 Se = 0.6053 F = 2.884

Bivariate model

$CCR_5 logIC_{50}$ = 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

$CCR_5 logIC_{50}$ = 0.895(±0.268) Ims – 0.683(±0.28)Ix + 3.14 (±1.3) EDC4 – 11.0608 **Eq (3)**

N = 21, r = 0.6696, Se = 0.5101, F = 4.606

Tetravariate model

$CCR_5 logIC_{50}$ = 11.34(±8.45) HOMO + 1.004(±0.274) Ims – 0.7305(±0.276) Ix + 5.403(±2.11) EDC4 – 17.25 **Eq (4)**

N = 21 r = 0.7101, Se = 0.4985, F = 4.068

5. Acknowledgment

Authors are very thankful to Dr. S.L. Garg Retrd. Principal Govt. Arts and commerce College Indore (M.P.) INDIA for providing facilities and motivation in the work.

6. References

[1] E A Berger, P M Murphy, J M Farber, Chemokine Receptors as HIV-1 Co receptors: Roles in Viral Entry, Tropism, and Disease. *Annu. Re*V. *Immunol.* **1999**, *17*: 657-700.

[2] A S Fauci, Host factors and the pathogenesis of HIV-induced disease. *Nature* **1996**, *384*:529-534.

[3] R I Connor, K E Sheridan, D Ceradini, S Choe, N R Landau, Change in Co receptor Use Correlates with Disease Progression in HIV-1-Infected Individuals. *J. Exp. Med.* **1997**, *18:* 621-628.

[4] F Cocchi, A L DeVico, A Garzino-Demo, S K Arya, R C Gallo, P Lusso, Identification of RANTES, MIP-1R, and MIP-1*â* as the Major HIV-Suppressive Factors Produced by CD8 + T Cells. *Science* **1995**, *270*: 1811-1815.

[5] S Imamura, Y Nishikawa, T Ichikawa, T Hattori, Y Matsushita, S Hashiguchi, N Kanzaki, Y Iizawa, M Baba, Y Sugihara, CCR5 antagonists as anti-HIV-1 agents. Part 3: Synthesis and biological evaluation of piperidine-4-carboxamide derivatives. *Bioorg. Med. Chem.* **2005**, *13*: 397-416.

[6] UNAIDS/WHO. *AIDS epidemic update: December **2004**;* World Health Organization: Geneva, Switzerland, **2004.**

[7] Shinichi Imamura, Takashi Ichikawa, Youichi Nishikawa, Naoyuki Kanzaki, Katsunori Takashima, Shinichi Niwa, Yuji Iizawa, Masanori Baba, and Yoshihiro Sugihara. *Journal of Medicinal Chemistry* 10.1021/jm051034q American Chemical Society Published on Web 04/05/2006

[8] H Sklenar and J Jager. International journal of quantum chemistry, **1979,** 16(3):467-484.

[9] K Tuppurainen, S Lotjonen, R Laatikainen, T Vartiainen, U Maran, M Strandberg, and T Tamm. Mutation research, **1991,** 247(1):97-102.