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QSAR Study on Novel CCR5 Receptor Antagonists: An Insight into the Structural Requirement for the HIV Co Receptor Antagonist Activity

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Abstract

Chemokines receptors have emerged as important drug targets for development of agents against the HIV/AIDS pandemic. With the purpose of designing new chemical entities with enhanced antagonistic potencies against the CCR5 chemokine receptor, the QSAR study carried out on 70 novel phenoxybenzyl derivatives as antagonists of CCR5 HIV co receptor is presented. The developed model was validated by standard QSAR parameters and through a detailed structural analysis on how it reproduces the quantitative differences observed in the experimentally known activity data. The model showed a good correlative and predictive ability having a cross validated correlation co-efficient (r^2_{cv}) of 0.708 and a conventional correlation coefficient (r^2) was found to be 0.805. The study revealed that the CCR5 antagonistic activity exhibited by the series is largely explained by steric factors of substituents emphasizing the role of size and shape of the inhibitors in making effective antagonist-CCR5 binding chemistry. A detailed investigation was made on the structural basis for the antiretroviral activity and the insights gleaned from the study could be usefully employed to design antagonists with a much more enhanced potency and selectivity.

Keywords

QSAR • HIV/AIDS • CCR5 • Phenoxybenzyls • TSAR

Introduction

Despite efforts to prevent the spread of human immunodeficiency virus (HIV), the worldwide population of HIV infected patients keeps alarmingly on the rise. The development of combination antiretroviral therapy comprised of reverse transcriptase inhibitors and protease inhibitors has provided a useful means of suppressing viral load in HIV infected subjects and has resulted in dramatic reductions in HIV associated morbidity and mortality [1]. However, none of the current therapies are curative [2] and HIV replicates rapidly when treatment ceases [3]. The complexity of the dosing regimens and the toxicity of the current antiretroviral therapy make it difficult to maintain patient compliance [4]. In addition, resistance to the currently available drugs is increasing [5]. Therefore, there remains a need to identify new classes of agents with improved efficacy and less toxicity.

The process of HIV entry into host cells is one of the attractive targets for inhibition of HIV replication [6]. Recent successful studies with enfuvirtide, a peptide inhibitor of gp41-mediated HIV entry, have confirmed this process as a clinically relevant target [7]. It has been reported that HIV strains that cause the initial infection predominantly utilize chemokine receptor 5 (CCR5) as a co receptor [8]. CCR5 is a member of the seven-transmembrane G-protein-coupled receptor superfamily [9]. The natural ligands for CCR5 are the chemokines, which have been reported to inhibit HIV infection *in vitro* [10]. Individuals homozygous for a defect in CCR5 expression have been identified as being highly resistant to HIV infection, while this defect does not cause a significant health problem [11–13]. In addition, infected individuals heterozygous for the defective gene appear to exhibit delayed disease progression [14]. Given the importance of HIV co-receptors in viral entry and replicative life cycle, chemokine receptors have become one of the most promising targets for antiretroviral drug discovery [15–21].

TSAR is an integrated analysis package for interactive investigation of quantitative structure-activity relationships [22–24]. It provides functions required to carry out any QSAR investigation whether in pharmaceutical, agrochemical, toxicological, or any other area of application. In common with all QSAR a method [25-28], it is based on a numerical description of molecular structure and employs statistics to obtain a correlation. Molecular structures are represented with a variety of 2D and 3D descriptors, the activity-descriptor relationship is computed by different standard statistical tools such as multiple regression, partial least square regression and neural network analysis, and the output is displayed in the form of a model highlighting substituent points that are strongly correlated with the pharmacotoxicological properties under investigation. The TSAR methodology assumes that a suitable sampling of these structural descriptors provides all the information needed for understanding their biological properties. TSAR has been employed to investigate the structural basis for the antiproliferative activity of aminophenylbenzamides and acrylamides [29]. Recently, researchers have applied TSAR to study the structural requirement for the antidepressant activity activity by theinpyrimidinone derivatives and found that that the 5-HT autoreceptor antagonistic activity exhibited by the series is largely explained by steric bulkiness of substituents [30]. Lohray et al. [31] have applied TSAR to analyse the structural requirement for the antibacterial properties of phenyloxazolidinone derivatives while Tronchet et al have applied TSAR to study the interaction of 6-phenylthiothymine derivatives with the HIV reverse transcriptase [32] These all may attest

the usefulness of such a methodology in understanding the structural requirements for the pharmacological properties of a given series.

The intense research on small molecule inhibitors of chemokine receptors has produced a diverse class of chemical scaffolds. Figure 1 shows some CCR5 antagonists. Although diverse in structure and large in number, most of them are beset with the problem of non-selectivity and weak binding affinity. TSAR, in common with other QSAR tools, is generally employed to enhance and optimize the binding affinity using a series of compounds acting on the same target with the same mechanism of actions. As a quantitative pharmacophore mapping tool, such a methodology is valuable in pinpointing the structural requirements for the observed pharmacotoxicological properties by the series. Such insights are an aid to design a new entity having an acceptable level of potency and selectivity. In this paper, we report the QSAR study carried out on 70 novel CCR5 antagonists in the anticipation of getting a model that would account for the quantitative differences in bioactivity seen in this series and to capitalize upon the insights to design ligands with pronounced inhibitory potency and selectivity.

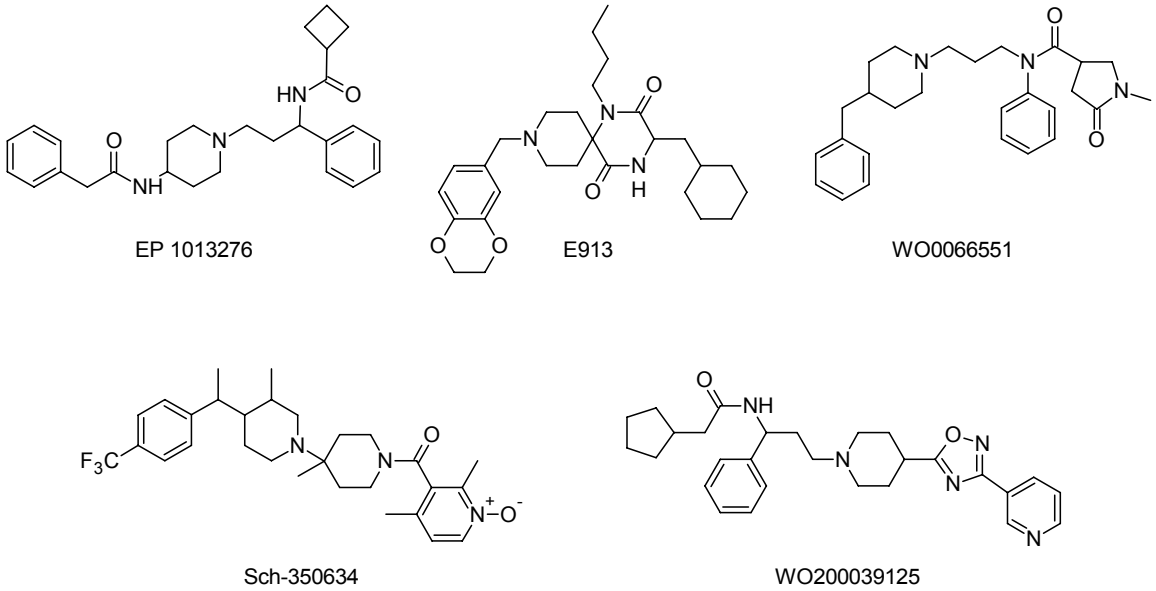


Fig. 1: Examples of CCR5 antagonists

Computational Details

Dataset for Analysis

The in vitro biological activity data reported as IC_{50} for inhibition of CCR5 co-receptors by a series of phenoxybenzyl derivatives [33, 34] was used for the current study. As biological activities are generally skewed, the reported IC_{50} values were converted into the corresponding pIC_{50} using the following formula:

$$pIC_{50} = -\log IC_{50}$$

Molecular Modeling

The structures of the phenoxybenzyl derivatives selected for the present QSAR study are shown in Table 2. The structures were sketched using ChemDraw ultra 8.0 and were exported to TSAR 3.3 software (www.accelrys.com). Three-dimensional structures of all the molecules were generated. Partial charges were derived using Charge-2 CORINA 3D package in TSAR 3.3 and their geometries were optimized using Cosmic module of TSAR. The calculations were terminated when the energy difference or the energy gradient were smaller than 1e-005 and 1e-010 kcal/mol respectively.

Molecular descriptors were calculated with TSAR 3.3. The descriptors were obtained for the substituents which vary from one molecule to another at a common point on the generic structure. TSAR affords calculation of the following descriptors: molecular surface area and volume, moments of inertia, ellipsoidal volume, verloop parameters, dipole moments, lipole moments, molecular mass, Wiener index, molecular connectivity indices, molecular shape indices, electrotopological state indices, logP, number of defined atoms (carbon, nitrogen, etc.), rings (aromatic and aliphatic), and groups (methyl, hydroxyl, etc.). Vamp which is a semiempirical molecular orbital package in TSAR 3.3 was used to calculate the electrostatic properties like total energy, electronic energy, nuclear repulsion energy, accessible surface area, atomic charge, mean polarizability, heat of formation, total dipole, polarizability, and dipole components. Structure optimization was performed in vacuo using default parameters with the AM1 Hamiltonian. Pairwise correlation analysis of the calculated descriptors was performed. The model was obtained using descriptors that are strongly correlated with the HIV entry blocking activity.

Statistical Analysis

The relationship between the structural parameters (TSAR descriptors) and the biological activities has been quantified by the multiple linear regressions implemented in TSAR 3.3. Values for F-to-enter and F-to-leave were set to 4. The cross-validation analysis was performed using leave-one-out (LOO) method where one compound is removed from the dataset and its activity is predicted using the model derived from the rest of the dataset. The cross-validated r^2 and conventional r^2 that resulted in lowest error of prediction was taken. Unless otherwise stated, the default values for the other TSAR QSAR parameters were used. The predictive capabilities of the QSAR model were determined using test set compounds that were excluded during model development. The structure generation, optimization, charge derivation, structural descriptor calculations and all other steps of the test sets were done in the same way with that of the training set compounds as described above, and their activities were predicted using the model produced by the training set.

Results and Discussion

The QSAR study was carried out using novel phenoxybenzyl derivatives which are reported as novel HIV entry inhibitors. Molecules, which lack biological inhibitory activity in numerical form, were removed from the analysis. Following this, 70 molecules were left for the present study. During the processes of model development and validation, two molecules were found not to fit to either the training set or test sets. Outliers generally exist when they posses a unique scaffold and hence act on a different receptor or when they act on a different binding site of the same receptor or because of the limitations on the quality of the biological data. But the structures of these molecules are not that unique to claim

that they bind differently. These too were removed and the remaining dataset was partitioned into a training set of 43 and a test set of 25 compounds at random with bias given to both chemical and biological diversity in both the training and test set molecules. Despite the ambiguity of drug–receptor interaction in general, a statistically significant model were obtained from the TSAR study.

The TSAR multiple regression analysis is summarized in Table 1. The cross-validated correlation coefficient defines the goodness of prediction whereas the non-cross-validated conventional correlation coefficient indicates goodness of fit of a QSAR model. The F-test value stands for the degree of statistical confidence. As it is evident from the body of table, a cross-validated correlation coefficient of 0.708 was obtained using leave-one-out cross-validation procedure. This indicates a very good internal predictive capability of the developed model. The model also exhibited a non-cross validated correlation coefficient of 0.805. The external predictive capability of a QSAR model is generally checked using test sets. All procedures including geometry optimization, charge computation, calculation of structural descriptors of the 25 test set molecules were done in a manner analogous to the training set molecules. The prediction of the test set molecules presented in Table 2 shows a satisfactory prediction indicating its usefulness in predicting activities of external molecules. Yet another way to further evaluate the usefulness of the developed model is to test for statistical stability. To this end, standard error of estimate and predictive residual sum of squares may be employed. The low values of standard error of estimate (0.299) and that of PRESS for training set (3.497) and test sets (7.897) further add to the statistical significance of the developed models. Table 3 shows the descriptors included in the final QSAR model and their statistical significance.

Tab. 1. Statistical parameters obtained for the TSAR model

QSAR Parameter	
No. of molecules in the training set	43
No. of molecules in the test set	25
r^2_{cv}	0.708
r^2	0.805
r	0.897
SEE	0.299
F-value	53.52
F probability	$2.105e^{-014}$
PRESS[a]	3.497
PRESS[b]	7.897

r^2_{cv} = Cross-validated correlation coefficient; r^2 = conventional correlation coefficient; SEE = standard error of estimate; PRESS[a] = predictive residual sum of squares for the training set; PRESS[b] = predictive residual sum of squares for the test set molecules

The structures of the inhibitors chosen and the actual and predicted activity are displayed in Table 2 while that of test sets is presented in Table 3. Figure 2 shows plots of actual versus predicted pIC_{50} values for the training set molecules. The histograms of residuals of the test set molecules is presented in Figure 3.

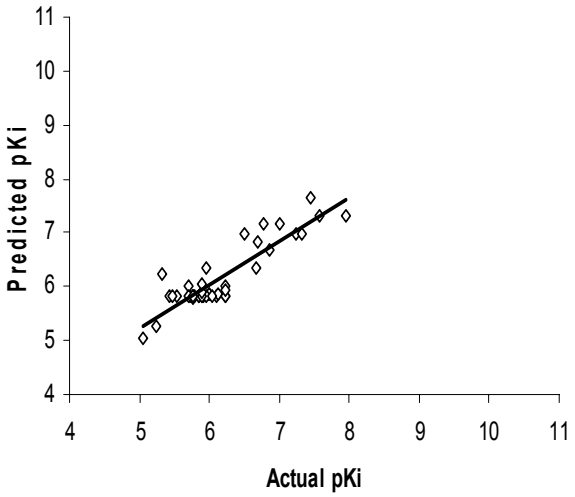


Fig. 2. Plots of actual versus predicted

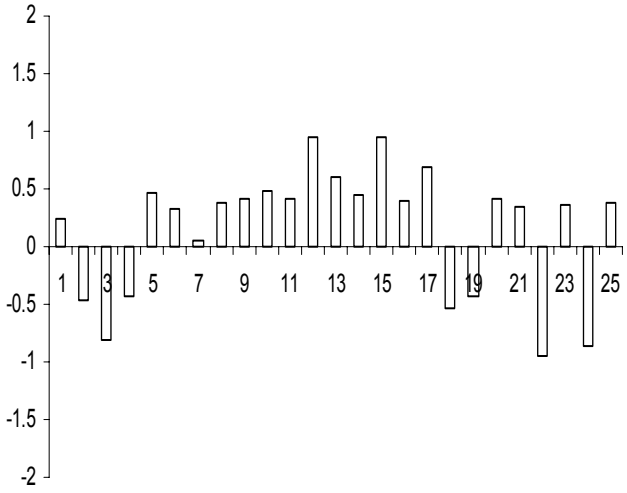
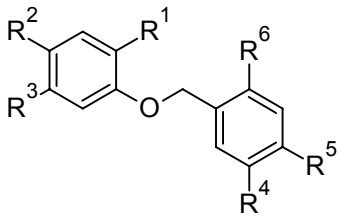
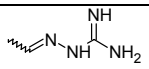
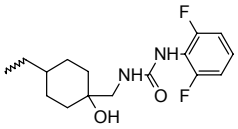
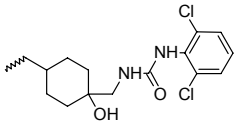
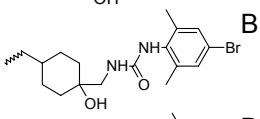
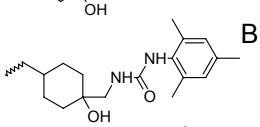
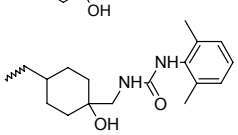
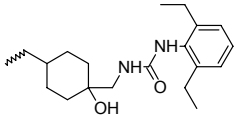
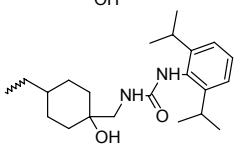
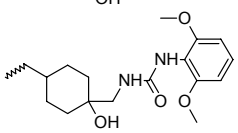
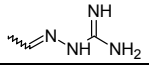


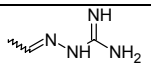
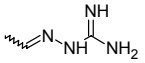
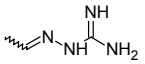
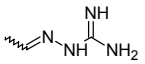
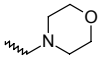
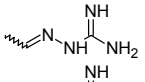
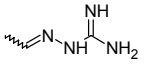
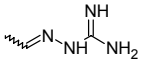
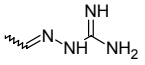
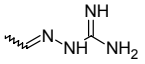
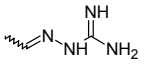
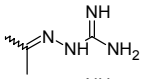
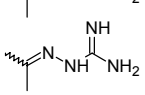
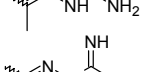
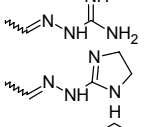
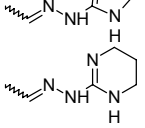
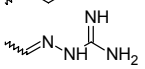
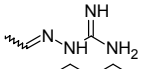
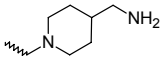
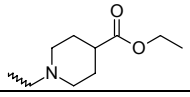
Fig. 3. Histograms of residuals of the test set molecules pK_i values for Training set molecules



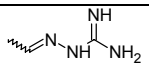
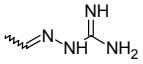
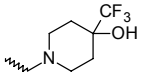
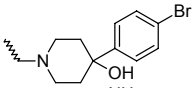
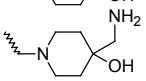
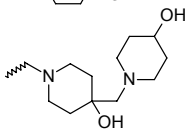
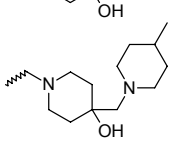
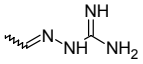
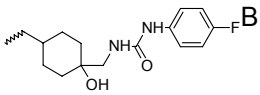
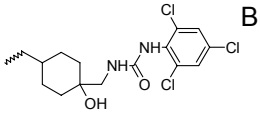
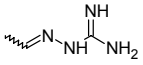
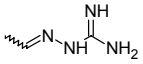
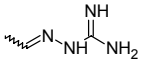
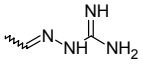
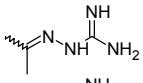
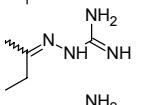
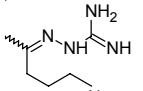
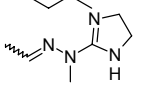
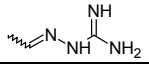
Tab. 2. Structures and the corresponding actual and predicted activities of the training sets.

No.	Antagonist Activity			Substitutions						Structural Descriptors		
	Act. pK_i	Pred. pK_i	Resid.	R^1	R^2	R^3	R^4	R^5	R^6	Verloop L	Verloop B1	Weiner Index
1	5.244	5.278	-0.034		Br	H	H	H	NO_2	3.54	1.65	32
2	6.495	6.996	-0.501		Br	H	H	Cl	H	2.09	1.65	1028
3	7.244	6.995	0.249		Br	H	H	Cl	H	2.09041	1.65	1028
4	6.770	7.161	-0.391		Br	H	H	Cl	H	2.08917	1.65	1170
5	7.000	7.161	-0.161		Br	H	H	Cl	H	2.08996	1.65	1170
6	7.328	6.996	0.332		Br	H	H	Cl	H	2.08957	1.65	1028
7	7.959	7.313	0.646		Br	H	H	Cl	H	2.088	1.65	1300
8	7.456	7.648	-0.192		Br	H	H	Cl	H	2.090	1.65	1588
9	7.569	7.313	0.256		Br	H	H	Cl	H	2.089	1.65	1300
10	5.886	5.834	0.052		Br	H	H	CO_2Me	H	2.094	1.65	32

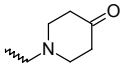
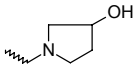
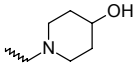
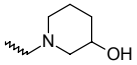
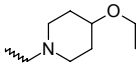
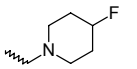
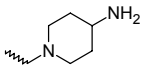
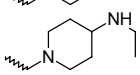
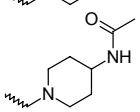
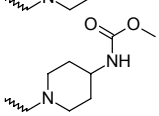
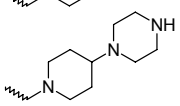
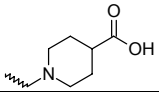
Tab. 2. (Cont.)

No.	Antagonist Activity			Substitutions						Structural Descriptors		
	Act. pK_i	Pred. pK_i	Resid.	R^1	R^2	R^3	R^4	R^5	R^6	Verloop L	Verloop B1	Weiner Index
11	5.796	5.835	-0.039		Br	H	CO_2Me	H	H	2.08978	1.65	32
12	5.770	5.836	-0.066		Br	H	Me	H	H	2.08917	1.65	32
13	5.538	5.835	-0.297		Br	H	H	OBn	H	2.0895	1.65	32
14	5.770	5.835	-0.065		Br	H	H	Ph	H	2.08965	1.65	32
15	6.000	5.847	0.153		Br	H	H	Cl	H	2.0897	1.65	42
16	5.432	5.836	-0.404		Br	H	F	F	H	2.08932	1.65	32
17	5.060	5.035	0.025		Br	H	NO_2	H	OMe	4.17935	1.65	32
18	5.921	5.836	0.085		NO_2	H	H	Cl	H	2.08861	1.65	32
19	5.468	5.835	-0.367		F	H	H	Cl	H	2.08995	1.65	32
20	6.222	5.836	0.386		CN	H	H	Cl	H	2.08882	1.65	32
21	5.721	5.835	-0.114		Br	H	H	H	H	2.08949	1.65	32
22	6.699	6.833	-0.134		Br	H	H	Cl	H	2.08953	1.74491	52
23	6.854	6.669	0.185		Cl	H	H	Cl	H	2.08966	1.72896	52
24	6.097	5.835	0.262		Br	H	H	F	H	2.08993	1.65	32
25	6.125	5.876	0.249		Br	H	H	Cl	H	2.08879	1.65	67
26	5.699	6.002	-0.303		Br	H	H	Cl	H	2.09059	1.65617	121
27	5.854	5.834	0.02	NEt_2	Br	H	H	Cl	H	2.08923	1.65	31
28	6.000	5.847	0.153		Br	H	H	Cl	H	2.0897	1.65	42
29	6.222	5.835	0.387		Br	H	H	Br	H	2.08962	1.65	32
30	5.770	5.800	-0.03	CH_2NH_2	Br	H	H	Cl	H	2.08911	1.65	1
31	5.959	5.810	0.149	CH_2NHEt	Br	H	H	Cl	H	2.09	1.65	10
32	5.854	5.834	0.02	CH_2NEt_2	Br	H	H	Cl	H	2.09009	1.65	31
33	5.886	5.828	0.058		Br	H	H	Cl	H	2.09003	1.65	26
34	5.699	5.835	-0.136		Br	H	CN	H	H	2.08986	1.65	32
35	5.886	5.903	-0.017		Br	H	H	Cl	H	2.08926	1.65	90
36	5.886	6.044	-0.158		Br	H	H	Cl	H	2.0904	1.65	211

Tab. 2. (Cont.)

No.	Antagonist Activity			Substitutions						Structural Descriptors		
	Act. pK_i	Pred. pK_i	Resid.	R^1	R^2	R^3	R^4	R^5	R^6	Verloop L	Verloop B1	Weiner Index
37	6.046	5.836	0.210		Br	H	H	NO_2	H	2.08875	1.65	32
38	5.770	5.835	-0.065		Br	H	NO_2	H	H	2.09033	1.65	32
39	6.237	6.011	0.226		Br	H	H	Cl	H	2.08974	1.65	183
40	5.319	6.220	-0.901		Br	H	H	Cl	H	2.09019	1.65	362
41	6.237	5.932	0.305		Br	H	H	Cl	H	2.08934	1.65	115
42	5.959	6.334	-0.375		Br	H	H	Cl	H	2.08942	1.65	460
43	6.678	6.334	0.344		Br	H	H	Cl	H	2.08917	1.65	460
44	6.076	5.835	0.241		Br	H	Cl	H	H	2.09	1.65	32
45	5.824	6.295	-0.471		Br	H	H	Cl	H	2.09	1.65	942
46	6.347	7.161	-0.814		Br	H	H	Cl	H	2.09012	1.65	1170
47	4.408	4.836	-0.428		Br	H	COOH	H	H	2.08891	1.65	32
48	6.301	5.836	0.465		Br	H	H	Me	H	2.08883	1.65	32
49	6.155	5.835	0.32		Br	H	H	OMe	H	2.08988	1.65	32
50	6.220	5.835	0.385		Cl	H	H	Cl	H	2.08999	1.65	32
51	7.032	6.974	0.058		Br	H	H	CN	H	2.08913	1.7586	52
52	6.398	6.017	0.381		Br	H	H	Cl	H	2.08981	1.66239	79
53*	5.377	12.192	-6.815		Cl	H	H	F	H	2.08995	2.25494	158
54*	4.850	6.691	-1.841		Br	H	H	Cl	H	2.08962	1.72691	89
55	6.222	5.809	0.413	NMe_2	Br	H	H	Cl	H	2.0895	1.65	9
56	6.319	5.835	0.484		Br	H	H	CN	H	2.09108	1.65	32

Tab. 2. (Cont.)

No.	Antagonist Activity			Substitutions						Structural Descriptors		
	Act. pK_i	Pred. pK_i	Resid.	R^1	R^2	R^3	R^4	R^5	R^6	Verloop L	Verloop B1	Weiner Index
57	6.222	5.809	0.413	CH_2NMe_2	Br	H	H	Cl	H	2.08949	1.65	9
58	4.996	5.945	-0.949	CH_2NMeBn	Br	H	H	Cl	H	2.08822	1.65	126
59	6.824	5.870	0.954		Br	H	H	Cl	H	2.08949	1.65	62
60	6.456	5.846	0.61		Br	H	H	Cl	H	2.0897	1.65	41
61	7.310	5.87	0.44		Br	H	H	Cl	H	2.08958	1.65	62
62	6.824	5.869	0.955		Br	H	H	Cl	H	2.0896	1.65	61
63	6.347	5.946	0.401		Br	H	H	Cl	H	2.09004	1.65	127
64	6.553	5.870	0.683		Br	H	H	Cl	H	2.08989	1.65	62
65	5.328	5.870	-0.542		Br	H	H	Cl	H	2.08957	1.65	62
66	5.509	5.946	-0.437		Br	H	H	Cl	H	2.08962	1.65	127
67	6.409	5.991	0.418		Br	H	H	Cl	H	2.09019	1.65	166
68	6.398	6.050	0.348		Br	H	H	Cl	H	2.08952	1.65	216
69	6.456	6.092	0.364		Br	H	H	Cl	H	2.09015	1.65	252
70	5.071	5.938	-0.867		Br	H	H	Cl	H	2.08999	1.65	120

Compounds 53* and 54* are outlying molecules

Tab. 3. Statistical significance of parameters in the TSAR derived model describing the antiHIV activity of phenoxybenzyl analogues

Parameter	Coffifients[a]	Jackknife SE[b]	Covariance SE[c]	t-value[d]	t-probability[e]
Verloop L (subs. 6)	-0.3828	0.0369	0.1215	-3.1510	0.0031
Verloop B1 (subst.1)	10.2653	2.6218	2.50722	4.0943	0.0002
Weiner topological index (subst.1)	0.0012	0.0001	0.0001	11.4072	5.4068e-014
Constant	-10.3396	4.34867			

[a]The regression coefficient for each variable in the equation; [b]An estimate of the standard error on each regression coefficient derived from a jack-knife procedure on the final regression model; [c]Gives an estimate of the standard error on each regression coefficient derived from the covariance matrix; [d]Measures the significance of each variable included in the final model; [e] Statistical significance for t-values.

The QSAR model with a high statistical significance is represented by Equation 1:

Eq. 1. $Y = -0.3828491X1 + 10.265334X2 + 0.0011649015X3 - 10.339647$

Where X1 is verloop length parameter of substituent 6, X2 is Verloop B1 of substituent 1 and X3 is Weiner topological index of substituent 1.

The statistics for this equation are shown in Table 1. As the model shows, the CCR5 blocking activity increases with an increase in the verloop B1 parameter and the weiner topological index of substituent 1 while the activity was found to decrease with an increase in the values for the verloop length parameter of substituent 6. The verloop parameters [35–37] are a set of multi-dimensional steric descriptors that define a box that can be used to characterize the shape and volume of the substituent which are very important in explaining the steric influence of substituents in the interaction of organic compounds with macromolecular drug receptors. The verloop B1-B5 parameters describe the width of the substituent in the direction perpendicular to the length of the substituent. The study suggests that CCR5 antagonistic activity is strongly correlated with variations in the substituents at two positions of the general skeleton: namely, substitution on an ortho position of the phenoxy moiety and another ortho position to the benzyloxy group. The QSAR model shows that substitution on the ortho position of the phenoxy scaffold is strongly correlated with the antiretroviral activity as it is evident from the higher verloop B1 parameter coefficient (10.265) of substituents in the developed model. The verloop L parameter, on the other hand, is found to negatively correlate with the antagonistic property. This apparently explains the difference in the activity of cpds **44** and **1** which differ only in their substitution on the ortho position of the benzyloxy moiety. Cpd **44** has got the higher activity for it showed a lower value for the negatively correlated length parameter at this position when compared to cpd **1**. The same reason appears to explain the lower activity of cpd **17** as compared to compounds **8, 9, 11–18, 20, 21, 47–50**. These are cpompounds which has got the same values for the descriptor used in the QSAR except the length descriptor. Cpd **17** has got the highest (4.179) value for the negatively correlated descriptor which appears to reduce its CCR5 antagonist activity. That the verloop B1 steric parameter is positively related with the bioactivity is what is evident from biological activities of cpds **22, 23, 51**. Cpd **51** has the higher activity as compared to **22** and **23** for it has a higher verlopp B1 parameter of the substituent that is positively correlated. Cpds with higher weiner's topological index for substituents at position 1 are showing a higher acticivity (see **cpds 5–9**) which is in harmony with the experimental know activity data. The QSAR suggests that of the six different points of substitution on the generic structure only variations on three points impact the activity greatly as shown in Figure 4. Considering the fact that the QSAR model was able to reproduce the experimental facts and that it was validated by the appropriate statistical procedures, it could be useful in designing more potent antagonists.

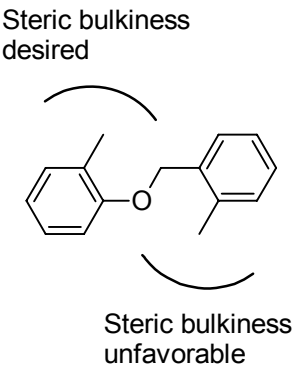


Fig. 4. Representation of regions where steric bulkiness is desired and undesired.

Conclusions

HIV co receptors have emerged as important drug targets with huge therapeutic potentials for their antagonists. The QSAR analysis using 70 phenoxybenzyl derivatives was successfully carried out to build a statistically significant model possessing a good correlative and predictive capability for the inhibition of CCR5 co receptor. The 2D-QSAR model was validated by standard statistical means and through observation on how it reproduces and explains the quantitative differences seen in the experimentally known activity data. The detailed structural investigation revealed that the antidepressant activity is predominantly explained by the steric factors of the substituent which govern the CCR5 antagonist-CCR5 interaction chemistry. The comparative investigation provided structural insights on how modulation of the steric bulk of the substituents could be usefully made to optimize the antiretroviral activity. The study provided useful clues about the structural requirement for effective antagonist-CCR5 interaction chemistry and hence for the improvement of the observed biological activity. This analysis could be of help in the rational design of potential drug candidates with an enhanced antagonistic potency.

Author's Statement

Competing Interests

The author declares no conflict of interest.

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