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3D QSAR Study on Alpha Keto Amide Derivatives as gp120-CD4 Inhibitors

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ABSTRACT
The present communication deals with 3D QDAR analysis on series of Alpha keto amide derivatives some for the designing of new GP120-CD4 inhibitors with anti HIV activity. The four different QSAR models are generated using data set of 32 molecules as gp120-CD4 inhibitors from literature studies. The 3D QSAR result gives insights for understanding of the relationship between structural features of substituted alpha keto amide derivatives and their activities which should be useful to design newer potential anti-HIV agents.

Keywords: Alpha keto amides, QSAR, MLR.

INTRODUCTION

Despite recent highly advanced techniques in retroviral therapy, need of novel potential chemical entity remains unsatisfied. HIV and related retroviruses belong to a class of enveloped fusogenic viruses. The viral envelope glycoproteins are organized in to oligomeric, probably trimeric spikes. The surface of spike is composed primarily of the exterior envelope glycoprotein gp120. As the first step in the life cycle of HIV, the gp120-CD4 interaction is an attractive target for rational drug design in prevention strategy. CD4 on mammalian cells acts as a host receptor and this interaction mediates attachment of virus to its target cells and plays an important role in host infection. [1-2] However, no approach to targeting the CD4-gp120 interaction has been successful in clinical practice. An *alpha* keto amide structure based small molecules had been reported as potent HIV entry inhibitors in cell cultures. [3-4] Recently discovered compound 1, the prototype of a series of novel HIV-1 entry inhibitors has directly gp120 binding ability. [3-5] Excitingly compound1 is active against both-R5, -X4 and dual tropic viruses and series of molecules based on compound1 have been also reported with gp120 binding activity. [3] The QSAR models plays key role in predicting activity of new molecules and provides interpretation of results, providing clues for designing new molecules. It makes recent drug design strategies more rational and advance. Evaluation of three dimensional molecular fields around molecules and generation of relationship of these fields' values with the activity comprises 3D QSAR study.

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MATERIALS AND METHODS

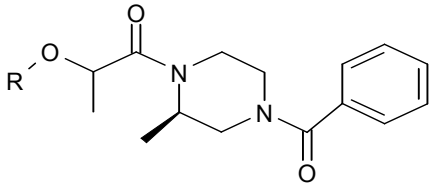
Data set

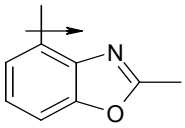
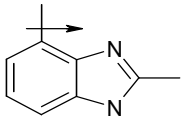
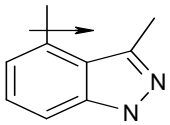
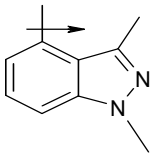
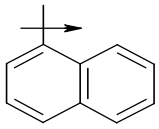
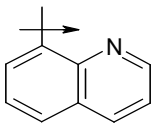
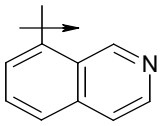
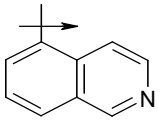
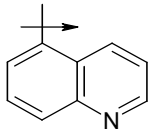
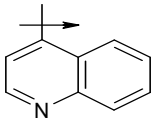
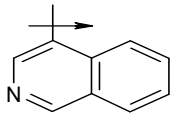
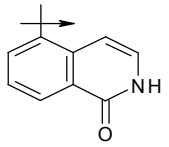
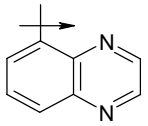
In the present work, data set of 32 molecules as a gp120-CD4 inhibitors were stressed from literature studies. [3] These compounds are alpha keto amides, mainly varies in methoxy pyridine amide and benzamide moieties of the prototype compound1. [3] The reported IC50 values (nM) from gp160 fusion assay of these compounds were converted to logarithmic values [pIC50 (nM)] [Table1].

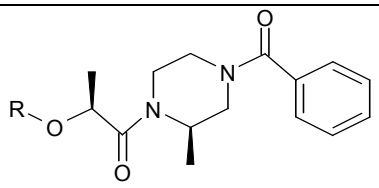
Computational studies

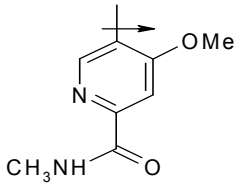
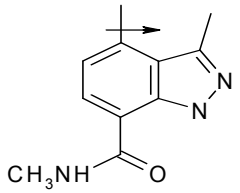
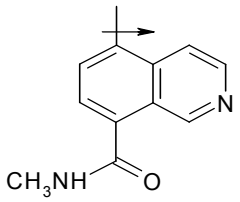
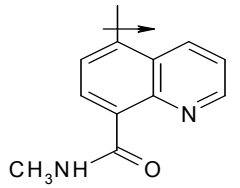
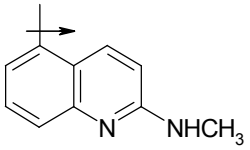
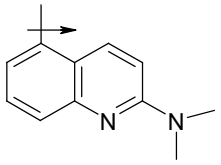
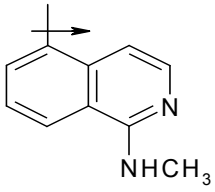
Molecular modeling and correlation analysis were executed on the Vlife software Molecular Design Suite (MDS) using 3.5 computer with Intel Pentium Dual Core Processor and Windows XP operating system. Structures were builded using 2D application tool and exported in 3D format. All 3D structures were geometrically optimized by minimizing energy. UFF force field method was used with dielectric constant 1.0 of medium (it is 1 for in vacuum), 1000 number of cycles and 1.0 as convergence criteria (root mean square gradient). Non-bonded cut off of 20 kcal/mol and 10kcal/mol for electrostatic and Vander Waal were applied. Alignment of optimized molecules was carried out using template based alignment method. Compound 10 was considered as reference molecule and structure—as template. The alignment of the molecules is shown in Fig. 1.

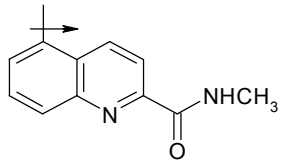
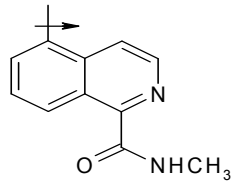
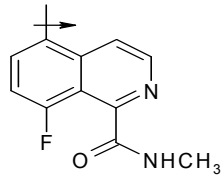
Table 1: structures of compounds and their gp160 fusion inhibitory activities

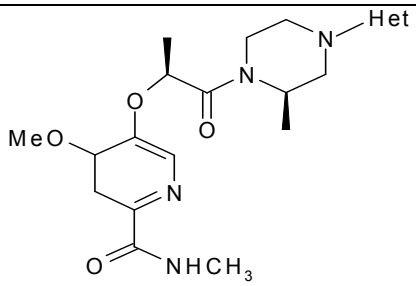


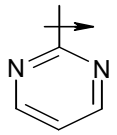
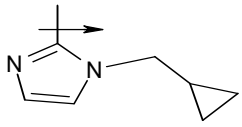
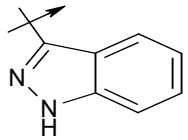
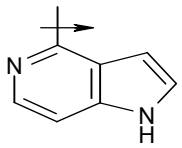
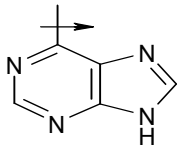
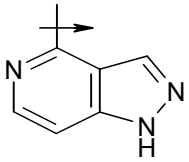
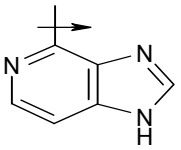
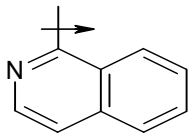
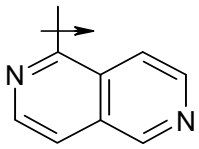
S. No	Compound	R	pIC50 (nM)
1.	3		-3.3098
2.	4		-2.92118
3.	5		-1.20412
4.	6		-1.17609
5.	7		-2.08991
6.	8		-2.63658
7.	9		-2.7597
8.	10		-2.01283
9.	11		-1.99564
10.	12		-3.86967
11.	13		-3.97062
12.	14		-1.83251
13.	15		-2.69293



14.	1		-1.146125
15.	19		-4.000000
16.	20		-4.3279
17.	21		-3.10018
18.	22		-0.69897
19.	23		-3.50446
20.	24		-1.78534

21.	25		-1.89208
22.	26		-1.32222
23.	27		-1.49136



S. No	Compound	Het	pIC50 (nM)
24.	29		-1.85124
25.	30		-3.27901
26.	31		-1.62324
27.	32		-1.4624
28.	33		-2.47134
29.	34		-1.38021
30.	35		-1.38021
31.	36		0.537602
32.	37		-1.4624

Descriptor calculation

All three fields electrostatic, hydrophobic and steric were computed at the lattice points of grid around aligned molecules in space. The values 10 kcal/mol and 30kcal/mol were used as cut-offs of electrostatic and steric respectively. Dielectric constant of medium was taken as 1. Methyl probe of charge +1.0 was used to compute interaction energies. At the end it provided how descriptors govern binding of each molecule at the active site in the form of numbers.

Data selection

In numerical data of different variables, activity and all the other descriptors were considered as dependent and independent variables respectively. Data set was categorized in to two parts, training set and test set. Only training set is exclusively used for building QSAR model. Generated model is applied to predict activity of test set to evaluate its predicting ability.Random and manual selection methods were used to generate training set and test set. In random selection method percentage of training set was 80%. Manual selection method was used after getting proper judgment from results of random selection trials. Manual selection method was exploited for the optimization of QSAR model

Model building

Once training set and test set defined, regression analysis between dependant and independent variables was done by using Multiple regression method. Multiple regression method is also called as ordinary least squares regression (OLS). Stepwise (SW) forward selection method was extensively used with cross correlation limit as 1 and 0.00 as variance cut-off.

RESULTS AND DISCUSSIONS

In the present study, training set and test set were created by random selection method and consequently by using random selection method. 25 to 24 molecules were used in the training set to derive QSAR models(table 2 and 3) with the number of field grid points being not more than four per model. To evaluate the predictive ability of generated 3D-QSAR models, a test set of 7 to 8 molecules with regularly distributed biological activities was used . A prerequisite for QSAR study is a congeneric series of molecules, all having the same mechanistic profiles with similar functional properties. Congenericity is a challenging task to define, though it is well-documented that all molecules in a set should have the same molecular framework with structural variation in one or several positions. Multiple regression

Table 2: Statistically significant models

Parameters	Model-1	Model-2	Model-3	Model-4
Training set size (Percentage)	25 (80%)	25 (80%)	24(75%)	25 (80%)
Test set size	7	7	8	7
Test set	20, 24, 32, 34, 36, 3, 9	12, 4, 19, 22, 21, 7, 11	22, 23, 24, 7, 8, 9, 14, 15	12, 14, 4, 8, 19, 35, 22
Degree of freedom	20	20	19	20
r^2	0.9009	0.8649	0.8864	0.8426
r^2se	0.3341	0.4296	0.3341	0.4652
q^2	0.8521	0.8084	0.8009	0.7667
F test	45.43	32.0061	37.0450	26.7570
Descriptor	S_953	E_91	E_666	E_1067
	E_209	S_356	S_515	S_753
	S_1034	S_1186	S_192	E_319
	S_575	E_307	S_615	S_443
Coefficient	-1.5466	-5.1717	-0.3449	0.0722
	3.4109	0.0381	4.0890	0.8491
	-0.0457	7.2440	-658.9540	1.3073
	-0.0355	1.1451	3.6039	-0.0909
Constant	-2.0979	-2.8315	0.9430	-2.1652
Parameters	Model-1	Model-2	Model-3	Model-4
Training set size (Percentage)	25 (80%)	25 (80%)	24(75%)	25 (80%)
Test set size	7	7	8	7
Test set	20, 24, 32, 34, 36, 3, 9	12, 4, 19, 22, 21, 7, 11	22, 23, 24, 7, 8, 9, 14, 15	12, 14, 4, 8, 19, 35, 22

Table 3: Observed, predicted activity and residuals (Model-1) of compounds.

S. No	Compound	Observed activity	predicted activity	Residuals
1	10	-2.01283	-2.31381	0.300984
2	11	-1.99564	-1.39215	-0.60349
3	12	-3.86967	-3.96917	0.099503
4	13	-3.97062	-3.84197	-0.12865
5	14	-1.83251	-1.66964	-0.16286
6	15	-2.69293	-2.84906	0.156125
7	16	-4	-4.02718	0.02718
8	19	-1.14613	-1.18436	0.038232
9	1	-4.3279	-2.51644	-1.81146
10	21	-3.10018	-2.67418	-0.426
11	22	-0.69897	-1.23078	0.53181
12	23	-3.50446	-3.21241	-0.29205
13	24	-1.78534	-0.65834	-1.12701
14	25	-1.89208	-1.70761	-0.18447
15	26	-1.32222	-1.62716	0.304935
16	27	-1.49136	-1.65746	0.166101
17	29	-1.85124	-2.02489	0.173651
18	30	-3.27901	-2.98243	-0.29659
19	31	-1.62324	-1.65988	0.036638
20	32	-1.4624	-1.93237	0.469975
21	33	-2.47134	-1.86687	-0.60447
22	34	-1.38021	-1.84897	0.468757
23	35	-1.38021	-1.60573	0.225521
24	36	0.537602	-1.48056	2.018166
25	37	-1.4624	-1.64077	0.178375
26	3	-3.3098	-2.79443	-0.51538
27	4	-2.92118	-3.52205	0.600866
28	5	-1.20412	-1.09267	-0.11145
29	6	-1.17609	-1.33453	0.158436
30	7	-2.08991	-1.92468	-0.16523
31	8	-2.63658	-2.61357	-0.02301
32	9	-2.7597	-2.05399	-0.70572

analysis (or OLS) was executed with the help of stepwise (SW) forward variable selection method. On successful runs of OLS, different sets of equations were generated and these equations were further analyzed statistically to select the best model. As shown in Table 4, four models were selected after screening various combinations of different descriptors. The model 3 and 4 are discarded on the basis of correlation coefficient.

Interpretation of QSAR Model

The model 1 (Eqa 1) describes the optimum structural features that are required for the gp120 binding and to inhibit gp120-CD4 interaction. The steric and electrostatic fields were calculated using the Tripos force field and Gasteiger-Marsili charges. A training set of 25 molecules, and a test set of 7 molecules was used as described earlier. The model was selected on basis of r^2, q^2, pred r^2, F test values. The r^2 value for model 1 was 0.9009. Variations of steric and electrostatic properties in the structural features of the compounds in the data set led to an increase or decrease in binding affinities and selectivity. The steric interaction fields are represented in green lattice points at S_953, S_1034 and S_575 (Fig.2) implies that the steric interactions along these lattice points are required to be addressed. Interaction at the points like S_953, S_103 and S_575 is negatively contributing, so the compounds which are having the bulky substituents at the benzamide aromatic ring can show the decreased activity. E_209 in blue color (Fig.4) is approximately three times more and positively contributed. Electrostatic potential at the methoxy pyridine amide moiety may enhance the activity.

pIC50 = -1.5466S_953+ 3.4109E_209 -0.0457S_1034 -0.0355S_575 -2.0979……. Eqa 1

The Model-2 (Eqa 2) shows 0.8649 r2 value. Descriptors E_91, S_356, S_1186 and E_307 are the variables which affect the binding ability of the molecule. E_91 in blue color (Fig.4) has negative influence, so electrostatic potential at the amide of methoxy pyridine should be suppressed to get maximum affinity. Both steric S_356 andS_1186 in green color (Fig.4) shows positive correlation. Bulky groups at lattice points in green color (Fig.4) are significant for binding. E_307 in blue color (Fig.4) is positively contributing on the methoxy pyridine amide.

pIC50 = - E_915.1717 + S_356 0.0381+ S_1186 7.2440+ E_3071.1451-2.8315. ……. Eqa 2

In this presented work we have indentified the important structural requirement of *alpha* keto amides for inhibition of GP -120. Four different QSAR models are generated by using MLR technique; two models are selected on the basis of all statistical coefficients. The both the models are showing similar results which can be use full for the designing of more potent GP-120 inhibitors.

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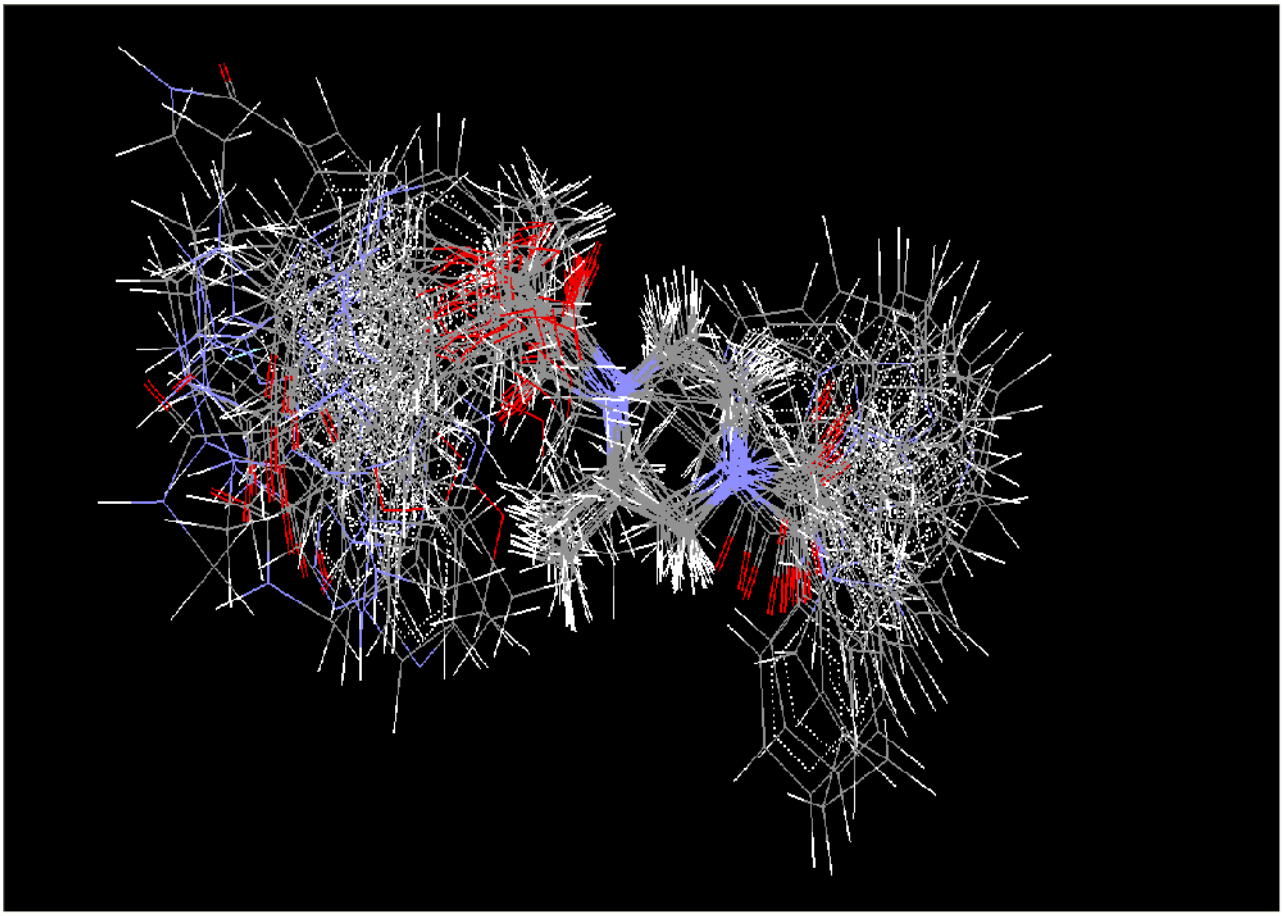

Fig. 1: Figure showing the alignment of the molecules

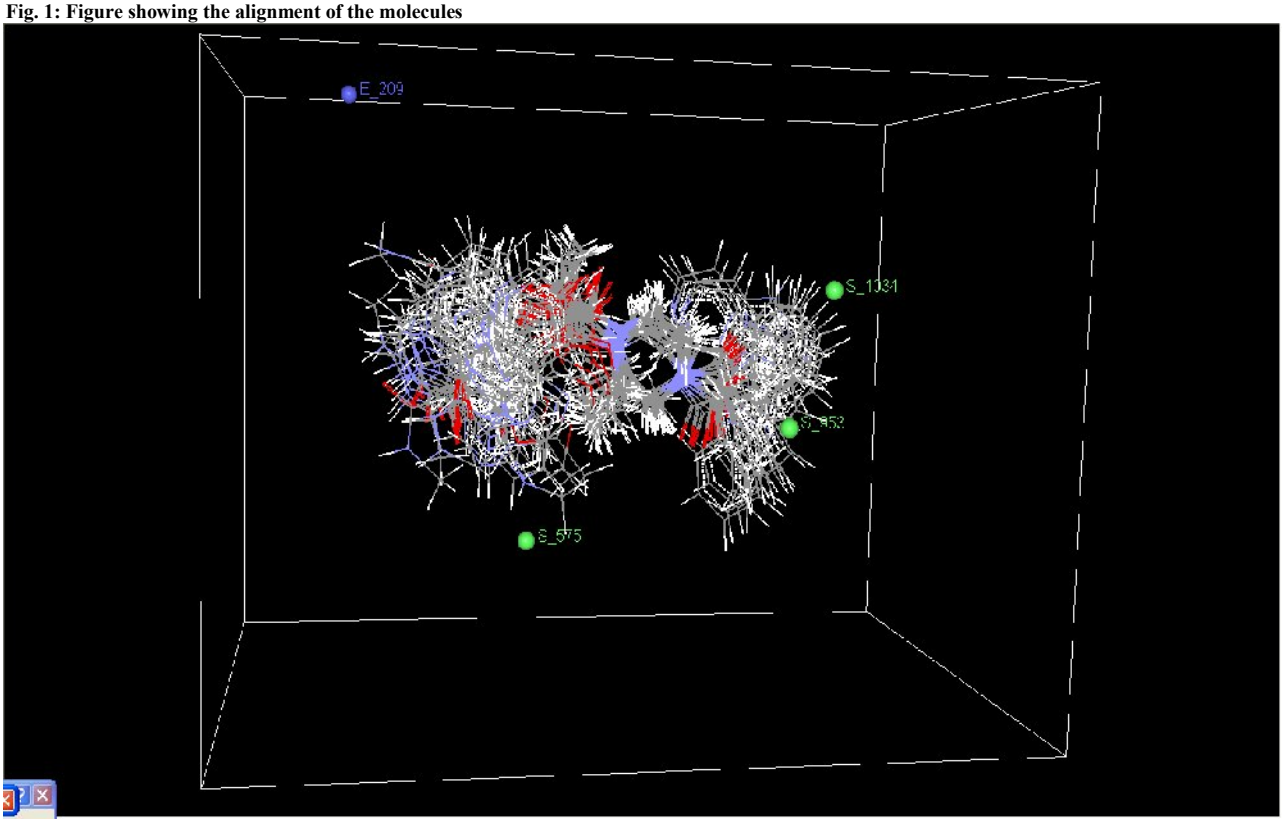

Fig. 2: MFA result (Show points): 3D-alignment of molecules with the important steric and electrostatic points contributing [Model 1] with ranges of values shown in parenthesis

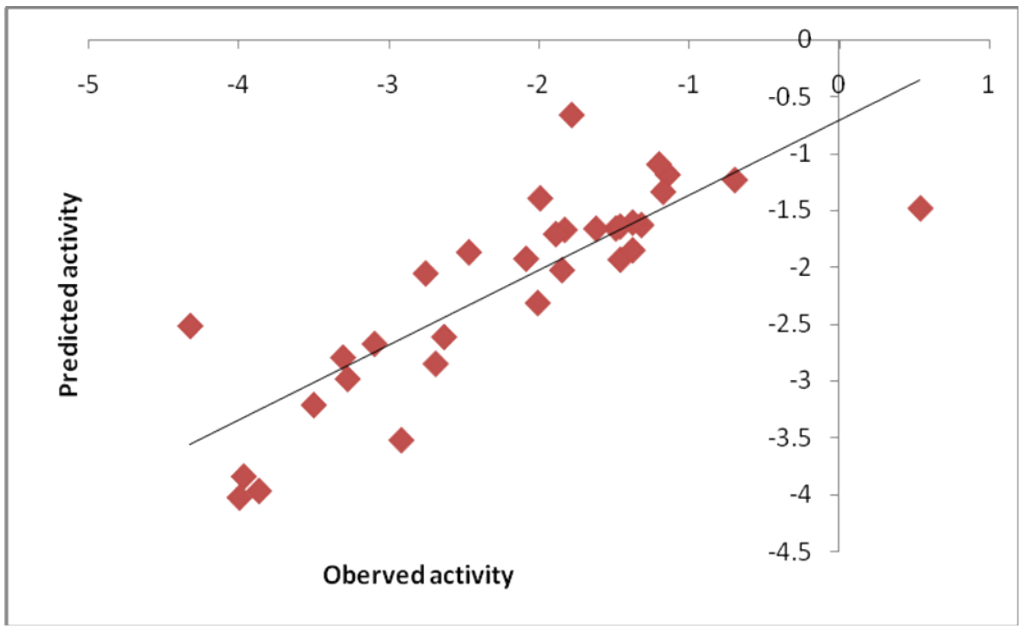

Fig. 3: Graph showing correlation between observed and predicted activity.

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