Quantitiative structure-activity relationship study of piperidine derived non-urea soluble epoxide hydrolase inhibitors

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ABSTRACT
A series of important amide non-urea inhibitors of soluble epoxide hydrolase (sEH) is disclosed. QSAR studies have been performed on forty-three molecules of derivatives. QSAR models have been evaluated for piperidine derivatives guided optimization of a lead compounds. In this work, we used multiple linear regression (MLR) procedure to derive 2D-QSAR models that show a strong correlation between piperidine derived non-urea soluble epoxide hydrolase inhibitors and various topological descriptors.

Key words: Non-urea inhibitors, SAR, MLR, QSAR

1 INTRODUCTION

Soluble epoxide hydrolase (sEH) may be a bifunctional homodimeric catalyst with hydrolase and enzyme activity detected in varied species starting from plants to mammals.[1] In humans it's principally situated in liver, kidney, internal organ and vascular tissues.[2] The sEH catalyst is selective for acyclic epoxides of fatty acids, and one among the foremost vital substrates is epoxyeicosatrienoic acid (EET).[3] EETs ar one among the metabolic derivatives of arachidonic acid.[4] The epoxygenase CYP2 enzymes turn the epoxydation of olefine bonds of arachidonic acid generating EETs.[5] EETs exhibit vasodilatory effects in varied arteries [6,7] and possess anti-inflammatory drug properties.[8] sEH mediates the addition of water to EETs, changing them to the corresponding diols—dihydroxyeicosatrienoic acids (DHETs), that show abolished or diminished biological activity.

The inhibition of this catalyst, so might represent a promising therapeutic strategy since it might result in elevated levels of EETs, that might then have helpful therapeutic effects on pressure and inflammation.[9] the foremost explored sEH inhibitors thus far ar urea-based compounds and various structure–activity relationship (SAR) studies crystal rectifier to discovery of many potent urea-based sEH inhibitors with IC50s within the lower nanomolar vary.[10,11] but, the ureabased inhibitors usually suffer from poor solubility and stability, that hinders their medical specialty use in vivo.[12,13] Amides, carbamates and thioureas are evaluated as different pharmacophores in an endeavor to enhance physical properties of urea-based inhibitors. during this report we have a tendency to disclose our efforts towards coming up with novel non-urea, amide-based inhibitors of

sEH. The underneath study compounds with the biological activity were taken from Stevan Pecic et. al. [14]

Table 1: The biological results for sulphonamide aryl hydroxamic acid

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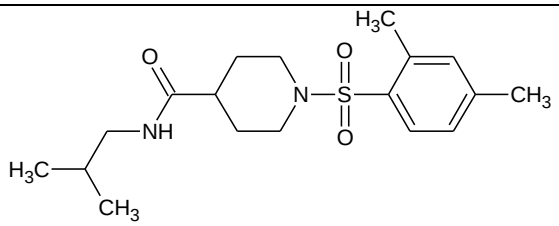
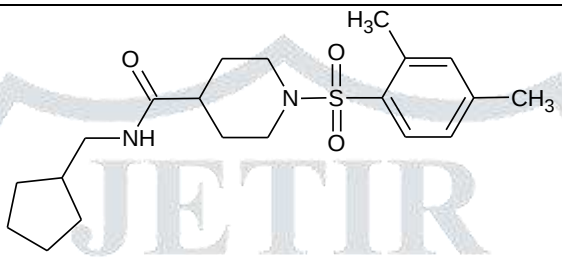
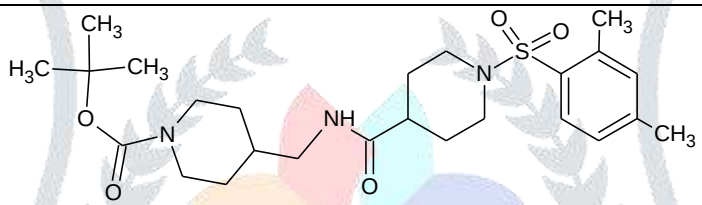
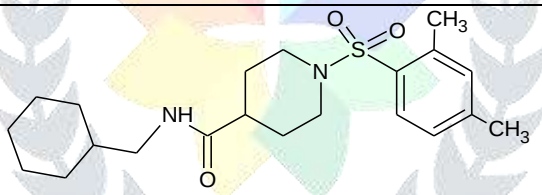
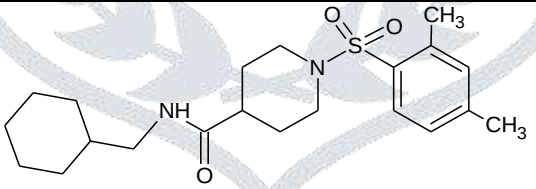
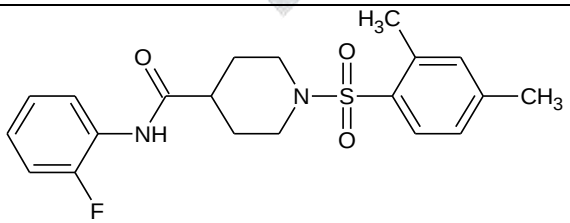
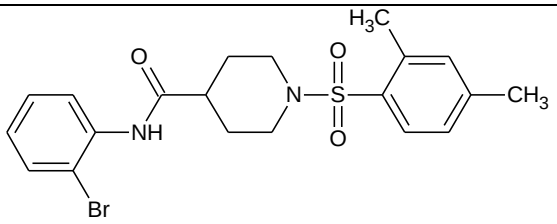
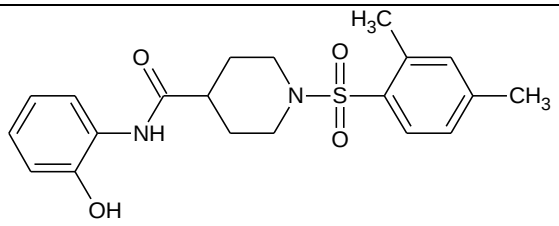
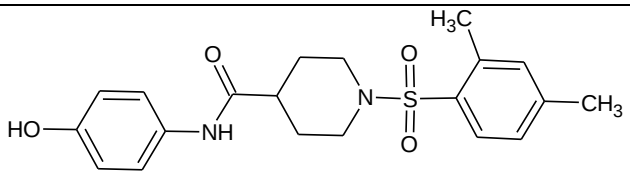
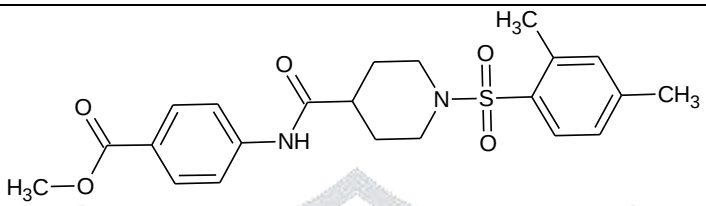
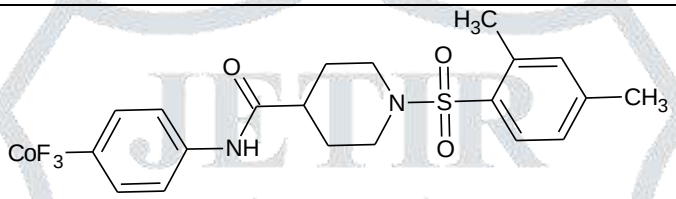
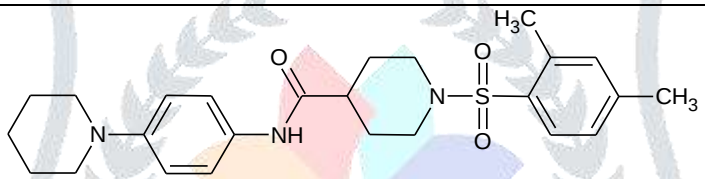
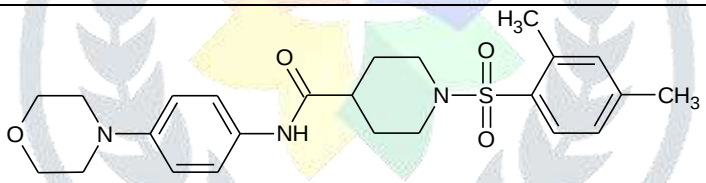
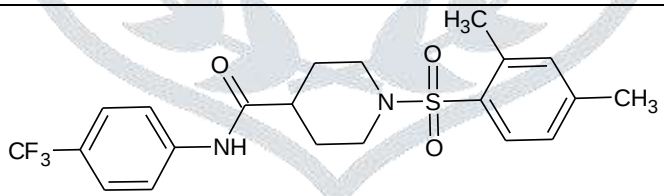
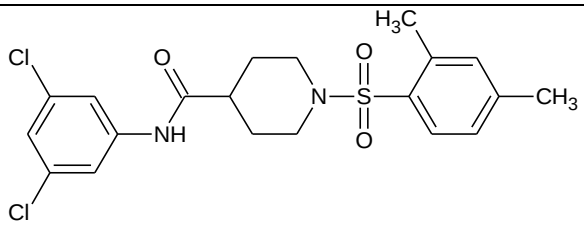
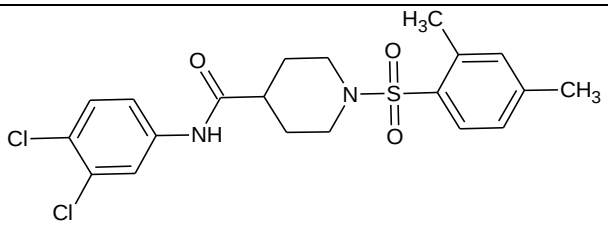
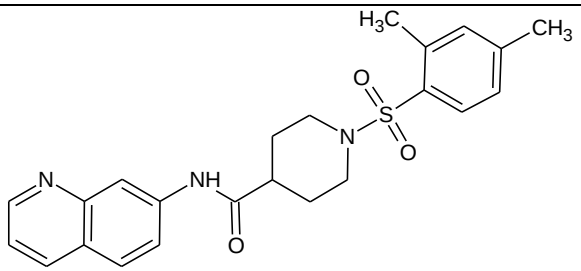
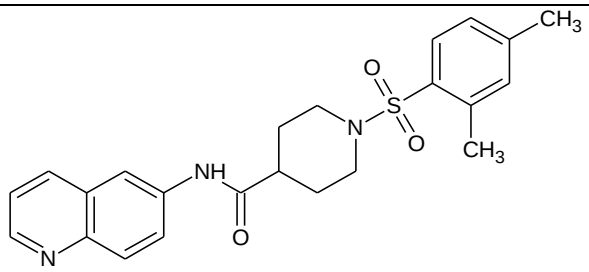
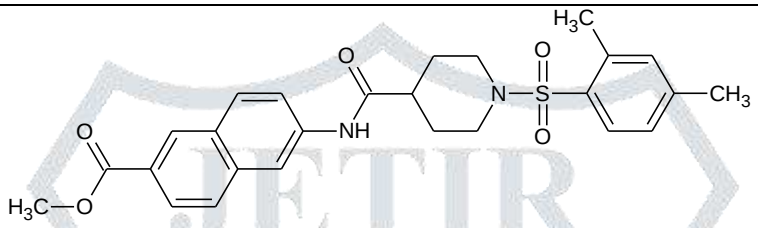
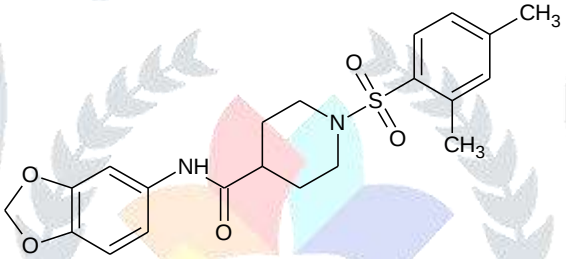
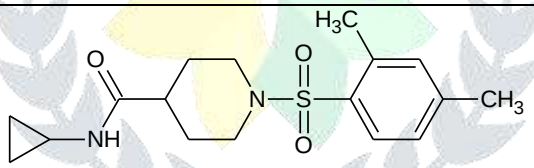
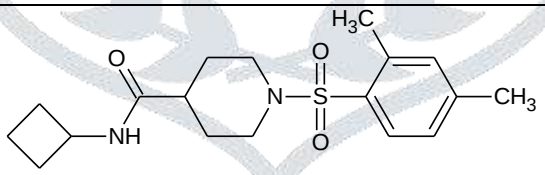
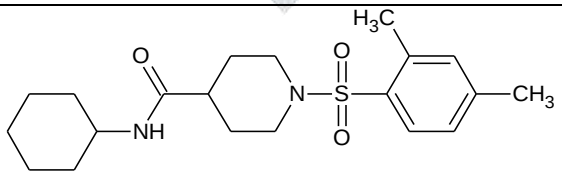
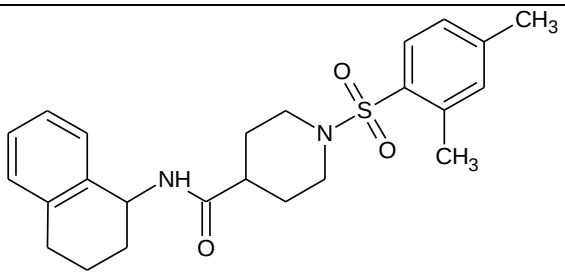
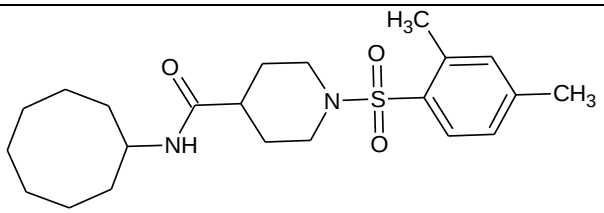
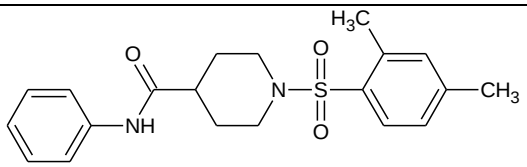
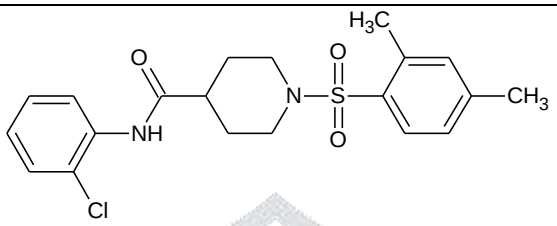
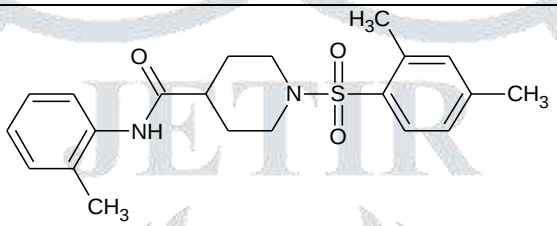
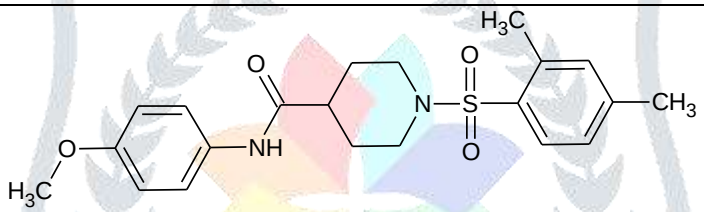
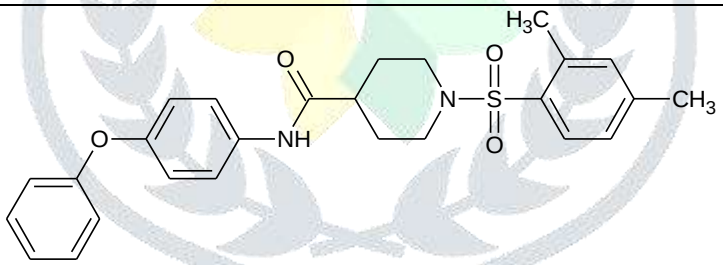
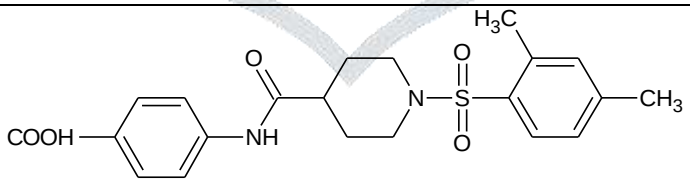
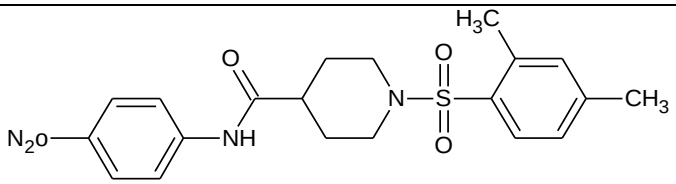
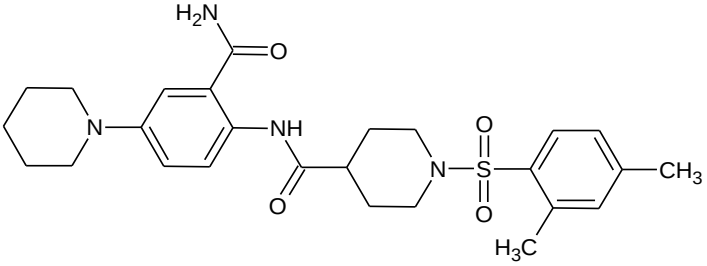
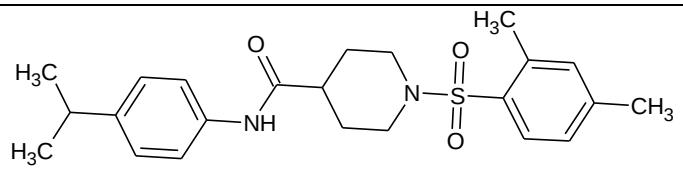
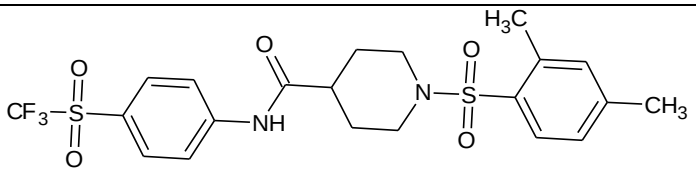
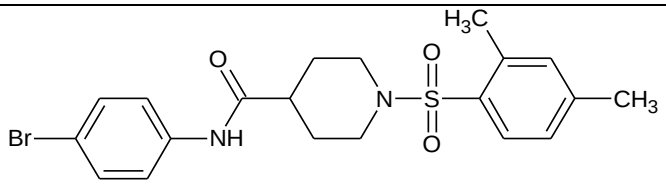
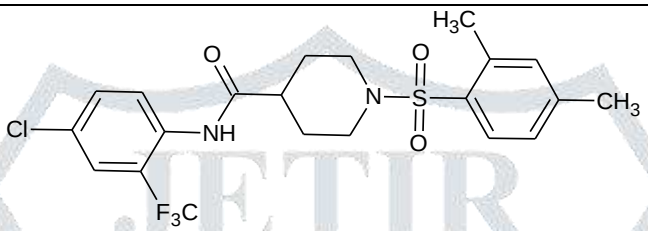
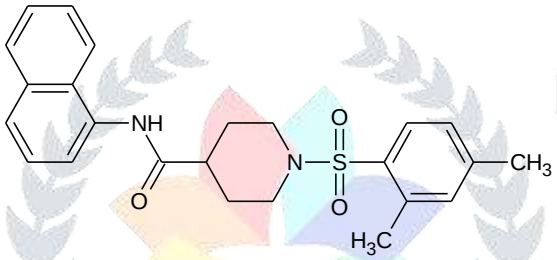
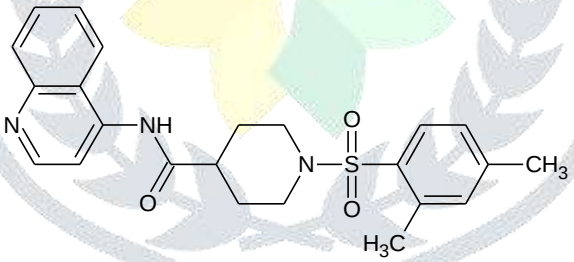
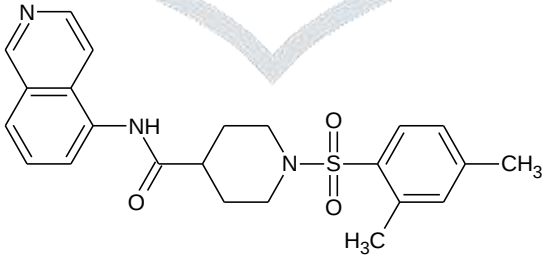
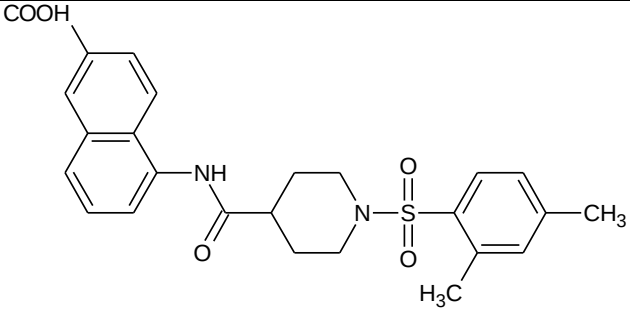
1		18
2		5.2
3		263
4		5.8
5		1.7
6		1.1
7		0.6

8		1.2
9		0.4
10		8.5
11		23
12		20
13		250
14		30
15		25
16		55

17		6.0
18		13
19		110
20		5.2
21		4.6
22		29
23		102
24		41

25		2.8
26		6.9
27		8.7
28		20
29		25
30		20
31		17
32		12
33		43

34		6.7
35		1.6
36		45
37		78
38		8.3
39		2.3
40		23
41		0.6

2. RESULTS AND DISCUSSION

Developing a QSAR model requires a diverse set of data, and thereby, a large number of descriptors have to be considered.[15] Descriptors are numerical values that encode different structural features of the molecules. A key step in QSAR modeling is evaluating model's stability and prediction ability. We used cross-validation and external test set for these proposes. Cross-validation has different variants such as leave-one-out (LOO), leave-group-out (LGO) and m-fold. It was shown previously that LOO can lead to chance and over fitted models whereas LGO is more sensitive to chance variables.

Table 2: Values of molecular descriptors used in regression analysis.

C.No.	IC_{50}	S_3K	BAC	BLI	MAXDN	ZM_2Kup	X_1A
1	18	3.486	54	0.871	5.239	469.895	0.449
2	5.2	3.314	26	0.858	5.215	517.895	0.442
3	263	5.458	85	0.816	5.32	697.03	0.441
4	5.8	3.601	26	0.854	5.226	533.895	0.444
5	1.7	3.601	26	0.854	5.226	533.895	0.444
6	1.1	3.405	37	0.848	5.279	555.229	0.441
7	0.6	3.607	37	0.93	5.227	535.629	0.441
8	1.2	3.358	37	0.85	5.269	545.532	0.441
9	0.4	3.497	37	0.85	5.254	545.532	0.44
10	8.5	4.056	52	0.832	5.289	616.805	0.444
11	23	3.488	37	0.854	5.24	533.895	0.44
12	20	4.024	26	0.83	5.261	646.121	0.438
13	250	4.09	26	0.822	5.266	669.394	0.438
14	30	3.488	37	0.854	5.24	533.895	0.44
15	25	4.07	50	0.914	5.255	559.621	0.439
16	55	3.917	50	0.914	5.252	559.621	0.439
17	6	3.455	26	0.837	5.252	608.712	0.435
18	13	3.455	26	0.837	5.251	608.712	0.435
19	110	4.163	52	0.821	5.301	696.805	0.437
20	5.2	3.301	26	0.827	5.254	628.441	0.433
21	4.6	2.86	26	0.871	5.174	469.895	0.435
22	29	2.756	26	0.866	5.19	485.895	0.438
23	102	3.314	26	0.858	5.219	517.895	0.442
24	41	3.33	26	0.842	5.253	597.895	0.435
25	2.8	3.916	26	0.851	5.243	549.895	0.446
26	6.9	3.314	26	0.858	5.219	517.895	0.442
27	8.7	3.534	37	0.887	5.24	538.758	0.441
28	20	3.348	37	0.854	5.249	533.895	0.441
29	25	3.713	38	0.842	5.254	573.168	0.444
30	20	4.486	26	0.826	5.271	669.168	0.44
31	17	3.488	37	0.854	5.24	533.895	0.44
32	12	3.488	37	0.854	5.24	533.895	0.44
33	43	4.378	51	0.818	5.351	711.166	0.438

34	6.7	3.82	51	0.848	5.265	565.895	0.441
35	1.6	4.181	66	0.959	5.308	612.649	0.437
36	45	3.755	37	0.93	5.224	535.629	0.44
37	78	3.725	50	0.883	5.264	554.758	0.439
38	8.3	3.33	26	0.842	5.253	597.895	0.435
39	2.3	3.339	26	0.837	5.257	608.712	0.435
40	23	3.339	26	0.837	5.256	608.712	0.435
41	0.6	3.498	37	0.839	5.271	613.895	0.434

Therefore, we used LGO for model-validation utilizing correlation coefficient and root mean square error of cross-validation as scoring function. In addition, an external test set composed of 24 molecules was also used. The molecules in this set did not have contribution in the model step and thus their predicted values can give a final prediction power of the models as measured by regression coefficient, standard error, fisher criterion, adjusted regression coefficient and cross validated regression coefficient.

First, separate stepwise selection-based MLR analysis were performed using different types of descriptors, and then, an MLR equation was obtained utilizing the pool of all calculated descriptors. MLR models for subsets of molecules (Table 4.1.3) provide the obtained equations for training set series of 39 compounds. In this series, the geometrical parameters did not represent a significant impact on the biological activity. The Calculated indices had a moderate impact on the HDAC inhibitory activity of according to a medium R^2 for the corresponding QSAR model. The equations obtained from topological and indicator descriptors were predictive. Pearson's correlation matrix has been performed on all descriptors by using **NCSS** 12.0 statistics software.

Table 3: Correlation Matrix Between Descriptors and Inhibitory Activity

	IC_{50}	**S_3K**	**BAC**	**BLI**	**MAXDN**	**ZM_2Kup**	**X_1A**
IC_{50}	1.0000						
S_3K	0.5757	1.0000					
BAC	0.3868	0.6800	1.0000				
BLI	-0.2413	-0.1018	0.2267	1.0000			
MAXDN	0.3231	0.7343	0.6206	-0.2760	1.0000		
ZM_2Kup	0.4502	0.6904	0.2683	-0.4794	0.8180	1.0000	
X_1A	-0.0186	0.169	0.2092	0.1304	-0.1276	-0.4211	1.0000

In QSAR study on the studied molecules, this compound has also detected as no outlier. (Table 4.1.5) describe the QSAR models resulted for 24 compounds using different

sets of descriptors. Again, among the groups of descriptors obtained from the whole molecular structure, the topological indices resulted in a significant QSAR model for predicting HDAC inhibitory activity of the studied molecules. It has a good statistical quality for predicting the activity of the inhibitors. The analysis of the matrix revealed six descriptors for the development of MLR models. The values of descriptors used in MLR analysis are presented in Table 4.1.1.

Model No.1

$$IC_{50} = -225.9833(\pm 59.2891) + 70.8233(\pm 16.10556)\ S_3K$$

n	r	Se	F-Ratio	R^2CV	Adj R^2
41	0.5757	47.51	19.338	0.1231	0.3143

From QSAR model No.1 the low statistical results indicates needs for the development of Biparametric or more multiparametric QSAR models follow by rule of thumb. Here, equations for topological descriptors were statistically acceptable. The effect of topological descriptors on the inhibitory activity sulfonamide derivatives of the compounds are described by QSAR Model No.1. The QSAR model no.1 has significant importance in which S_3K has positive contribution with the IC_{50} inhibitory activity.

Model No.2

$$IC_{50} = 64.2457(\pm 212.4396) + 68.5109(\pm 15.9820)\ S_3K - 328.8767(\pm 231.4121)\ BLI$$

n	r	Se	F-Ratio	R^2CV	Adj R^2
41	0.6043	46.900	10.931	0.1361	0.3318

Model No.3

$$IC_{50} = 3130.9727\ (\pm 1846.072) + 97.1128(\pm 23.1646)\ S_3K - 446.9083(\pm -446.9084)\ BLI$$

– 584.4829 (±-584.483) MAXDN

n	r	Se	F-Ratio	R^2CV	Adj R^2
41	0.6401	45.8309	8.564	0.1829	0.3619

The QSAR model No.2 and QSAR model No.3 show their significant statistical importance with biparametic and triparametric model in which BLI and MAXDN is inversely proportional with the IC_{50} inhibitory activity while S_3K is directly proportional with the IC_{50} inhibitory activity.

Model No.4

IC_{50} = 4509.4859 (±2056.668) + 82.5614(±24.97) S_3K - 649.7552(±272.78) BLI
- 812.7006(±379.39) MAXDN + 1.2799(±0.8895) BAC

n	r	Se	F-Ratio	R^2CV	Adj R^2
41	0.6647	45.18	7.126	0.1230	0.3799

Model No.5

IC_{50} = 9102.9147 (±2782.14) + 42.9153(±29.1922) S_3K - 500.4046(±265.757) BLI
- 1768.6708(±547.90)MAXDN + 2.7593(±1.0571)BAC
+ 0.6800(±0.2947)ZM_2Kup

n	r	Se	F-Ratio	R^2CV	Adj R^2
41	0.7180	42.69	7.450	0.2501	0.4464

The above described all models are not statistically excellent indicates the deletion of outliers compounds whose activity are not uniform and after deleting the compound no. 13 and 23 resulting the development of high statistically QSAR model no.5 indicates the importance of topological descriptors in IC_{50} inhibitory activity.

After deleting compounds no. 13 and 23

QSAR Model No.5

IC_{50} = 7732.8856(±1585.535) + 19.7891(±16.755) S_3K - 479.5779(±150.77) BLI
- 1487.2284(±312.526) MAXDN + 3.5259(±0.6055) BAC
+ 0.5450(±0.1695) ZM_2Kup

n	r	Se	F-Ratio	R^2CV	Adj R^2
39	0.8665	24.19	19.895	0.4144	0.7131

The randomization test suggests that the developed model have a probability less than 1% that the model is generated by chance. The observed IC_{50} activity and Predicted IC_{50} activity along with residual values are shown in Table 4. The plot of observed vs. Predicted activity is shown in figure 2. From the plot it can be seen that the MLR model is able to predict the activity of set of compounds as well as external.

The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy to compute descriptors in determing biological activites, which could shed light on the key factors that may aid in design of novel potent molecules.

Table 4: Values of Regression Analysis

Model No.	Parameters Used	Ai (1.....3)	Intercept	Se	R	Adj R^2
1	**S_3K**	70.8233 (±16.10556)	-225.9833 (±59.2891)	47.51	0.5757	0.3143
2	**S_3K**	68.5109 (±15.9820)	64.2457 (±212.4396)	46.90	0.6043	0.3318
	BLI	- 328.8767 (±231.4121)				
3	**S3K**	97.1128 (±23.1646)	3130.9727 (±1846.072)	45.8309	0.6401	0.3619
	BLI	- 446.9083 (±-446.9084)				
	MAXDN	– 584.4829 (±-584.483)				
4	**S3K**	+ 82.5614 (±24.97)	4509.4859 (±2056.668)	45.18	0.6647	0.3799
	BLI	- 649.7552 (±272.78)				

	MAXDN	- 812.7006 (±379.39)				
	BAC	1.2799 (±0.8895)				
5	**S3K**	42.9153 (±29.1922)	9102.9147 (±2782.14)	42.69	0.7180	0.4464
	BLI	- 500.4046 (±265.757)				
	MAXDN	- 1768.6708 (±547.90)				
	BAC	2.7593 (±1.0571)				
	ZM2Kup	0.6800 (±0.2947)				
After Deleting Compound No. 13 and 23						
6	**S3K**	19.7891 (±16.755)	7732.8856 (±1585.535)	24.19	0.8665	0.7131
	BLI	- 479.5779 (±150.77)				
	MAXDN	- 1487.2284 (±312.526)				
	BAC	3.5259 (±0.6055)				
	ZM2Kup	0.5450(±0.1695)				

Table 5: Experimental and predicted activities IC_{50} of the molecules under study

Com. No.	**Exp. IC_{50}**	**Predicted IC_{50}**	**Residual**
1	18.0	39.09694	-21.0969
2	5.20	5.058338	0.141663
3	263	217.142	45.85798
4	5.8	5.017797	0.782204
5	1.7	5.017797	-3.3178
6	1.1	-24.3925	25.49251
7	0.6	6.931919	-6.33192
8	1.2	-16.6951	17.89506

9	0.4	8.364057	-7.96406
10	8.5	67.7438	-59.2438
11	23.0	20.74581	2.254188
12	20.0	34.01696	-14.017
13	30.0	20.74581	9.254188
14	25.0	41.03981	-16.0398
15	55.0	42.47377	12.52623
16	6.0	12.39429	-6.39429
17	13.0	13.88152	-0.88152
18	110	100.8958	9.10421
19	5.2	21.92186	-16.7219
20	4.6	24.65237	-20.0524
21	29.0	9.91773	19.08227
22	41.0	0.139466	40.86053
23	2.80	-3.8716	6.671598
24	6.90	-0.89058	7.790576
25	8.70	8.480734	0.219266
26	20.0	4.590282	15.40972
27	25.0	35.06474	-10.0647
28	20.0	42.76788	-22.7679
29	17.0	20.74581	-3.74581
30	12.0	20.74581	-8.74581
31	43.0	36.52963	6.470373
32	6.70	59.81814	-53.1181
33	1.60	28.15159	-26.5516
34	45.0	14.32239	30.67761
35	78.0	33.04374	44.95626
36	8.30	0.139466	8.160534
37	2.30	2.662612	-0.36261
38	23.0	4.14984	18.85016

39	0.60	25.63923	-25.0392

The values obtained from the descriptors calculations explain the structural parameters and the possible interaction with the binding site of IC_{50} inhibitors

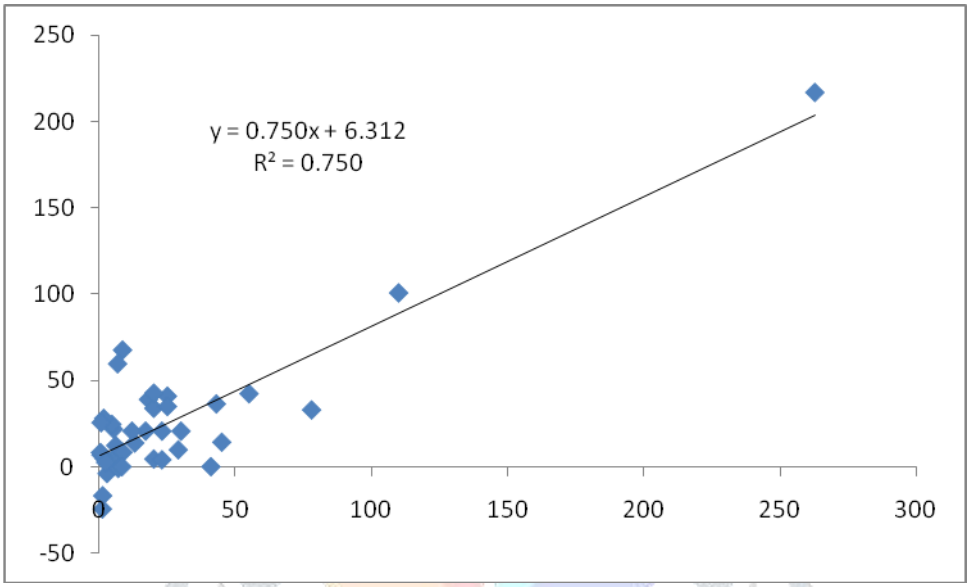


Figure 1. Plot of predicted versus experimentally observed inhibitory activity of under study molecules

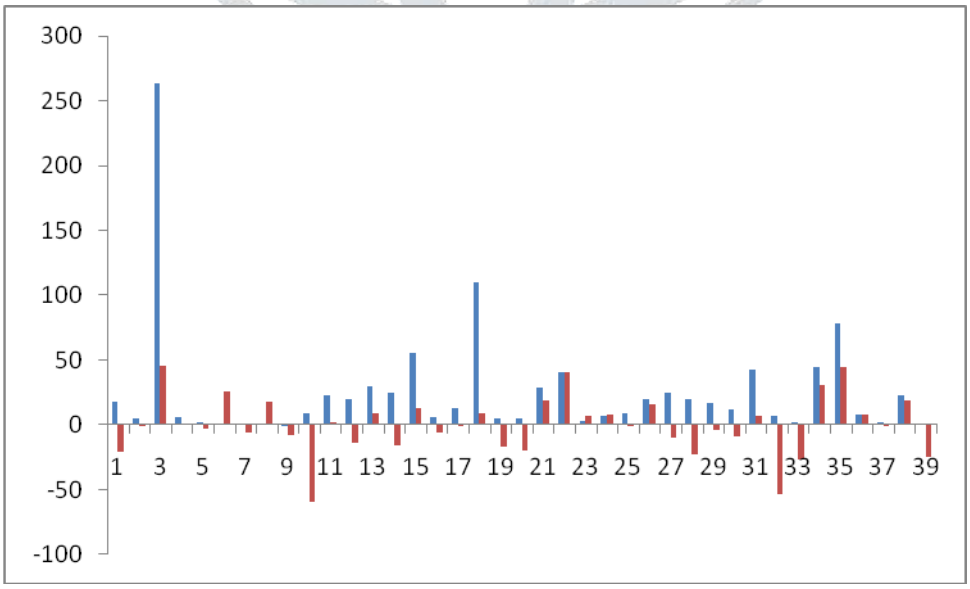


Figure 2. Plots of residual against experimental values log ($1/IC_{50}$).

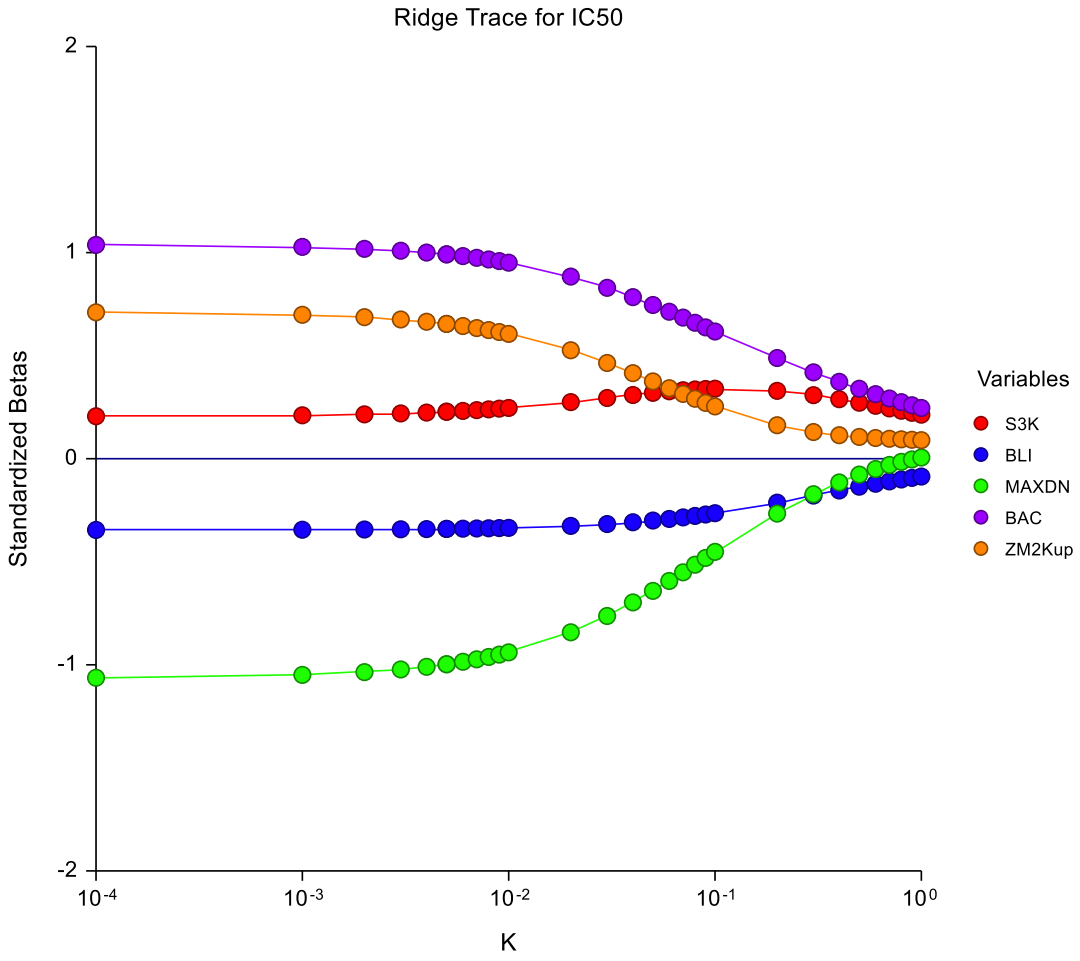


Figure 3: Ridge Regression between Descriptors and Biological Activity

CONCLUSION

Structure–activity relationship of the lead reveals some particular structural requirements to the left hand side part of the piperidine amide base sEH inhibitors.

1. A varying degree of bulky, non- polar cycloalkyl rings are well tolerated in this region by target enzyme.
2. Proper substitution on the phenyl ring is crucial for attaing good potency, emphasizing the importance of the small non polar groups and halogens in para position as a recognition element of sEH.
3. The left hand side phenyl is in a relatively close proximity to a several hydrophobic residue located in the large, nonpolar pocket of sEH that opens towards solvent, and probably participating in a pi stacking interaction with them.

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