

## Original article

**QSAR studies on structurally similar oxalyl aryl amino benzoic acid derivatives as antidiabetic agents**

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**Abstract**

QSAR (Quantitative structure-activity relationship) analysis based on classical Hansch approach was adopted on recently reported novel series of modified oxalyl aryl amino benzoic acid derivatives as antidiabetic agents. The regression analysis demonstrated that molecular descriptors are important in describing antidiabetic activity of modified oxalyl aryl amino benzoic acid derivatives.

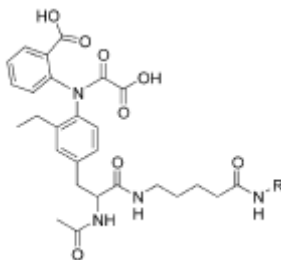
**Keywords:** QSAR, modified oxalyl aryl amino benzoic acid derivatives, molecular descriptors, antidiabetic activity

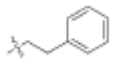
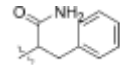
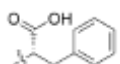
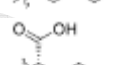
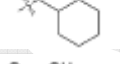
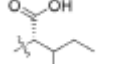
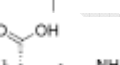
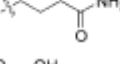
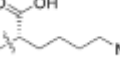
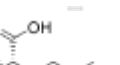
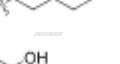
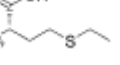
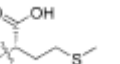
**Introduction**

Protein Tyrosine Phosphatases (PTPases) that function as negative regulators of the insulin signaling cascade have been identified as novel target for the therapeutic enhancement of insulin action in insulin resistant disease states<sup>7,10</sup>. Recent studies have provided compelling evidence that PTP1B is primarily responsible for dephosphorylation of insulin receptor and therefore acts to down regulate insulin signaling<sup>1-3, 11</sup>. A PTP1B inhibitor would be expected to increase half life of phosphorylated insulin receptor and enhance the effects of insulin. The development of PTP1B inhibitors began in early 1990s and continues today<sup>6, 8</sup>. T-cell PTPase (TCPTP), the most homologous phosphatase to PTP known to date, is implicated in regulating T-cell activation. Therefore selective inhibition of PTP1B without antagonizing TCPTP is highly desirable for an antidiabetic agent<sup>12</sup>.

Quantitative structure-activity relationship models are highly effective in describing the structural basis of biological activity<sup>4</sup>. It is now widely used for the prediction of physicochemical properties and biological activities in chemical and pharmaceutical areas<sup>13</sup>. The success of QSAR approach can be explained by insight offered into structural determination of chemical compounds and possibility to estimate the properties of chemical compounds without need to synthesize all and test them<sup>5</sup>.

In view of above and as part of our effort to create QSAR models that show substantial predictive promise, in the present study we report QSAR study on antidiabetic activity of series of oxalyl aryl amino benzoic acid derivatives reported by Xin *et al.*<sup>12</sup> as shown in Fig1 and Table1 and modified compounds as shown in Fig1b.

**Table1.** Chemical structure with antidiabetic potential of structurally similar oxalyl aryl amino benzoic acid derivatives.

**Fig1**

Comp. No.	R'	Ki ( $\mu\text{m}$ ) PTP1B
1.		3.4 ( $\pm$ 0.9)
2.		1.3 ( $\pm$ 0.4)
3.		0.14 ( $\pm$ 0.02)
4.		0.25 ( $\pm$ 0.10)
5.		0.43 ( $\pm$ 0.2)
6.		0.33 ( $\pm$ 0.16)
7.		0.71 ( $\pm$ 0.28)
8.		0.12 ( $\pm$ 0.07)
9.		0.13 ( $\pm$ 0.01)
10.		0.076 ( $\pm$ 0.015)
11.		0.47 ( $\pm$ 0.19)
12.		0.54 ( $\pm$ 0.19)
13.		1.7 ( $\pm$ 0.7)

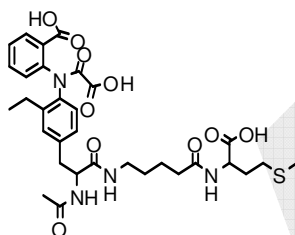
## Methods

### Antidiabetic activity

The binding affinity values were adopted from the work of Xin *et al.* We have used these values for QSAR model development.

### Selection of QSAR molecules:

A set of 63 inhibitors as shown in Fig.1b were designed in Chem office software from most active oxalyl aryl amino benzoic acid derivative found from literature<sup>12</sup> whose structure is shown in Fig1a (10<sup>th</sup> compound in Table1). The active molecule was modified from positions a, b, c and d as shown in Fig.1b.



Chemical Formula: C<sub>32</sub>H<sub>40</sub>N<sub>4</sub>O<sub>10</sub>S

Exact Mass: 672.25

Molecular Weight: 672.75

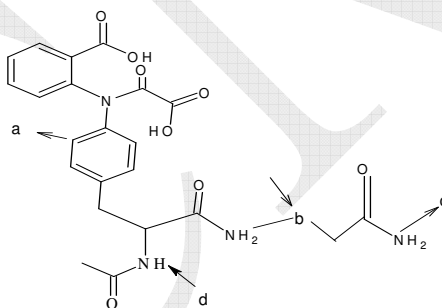
m/z: 672.25 (100.0%), 673.25 (36.3%), 674.25

(8.8%), 674.24 (4.5%), 675.25 (2.5%), 673.24 (1.5%)

Elemental Analysis: C, 57.13; H, 5.99; N, 8.33; O,

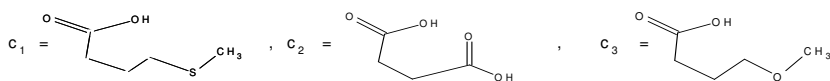
23.78; S, 4.77

Figure 1a (Active Molecule)



a<sub>1</sub>=H, a<sub>2</sub>=CH<sub>4</sub>, a<sub>3</sub>=CH<sub>3</sub>CH<sub>3</sub>, a<sub>4</sub>=CH<sub>3</sub>CH<sub>2</sub>CH<sub>3</sub>, a<sub>5</sub>=CH<sub>3</sub>CH(CH<sub>3</sub>)<sub>2</sub>

b<sub>1</sub>=(CH<sub>2</sub>)<sub>2</sub>, b<sub>2</sub>=(CH<sub>2</sub>)<sub>3</sub>, b<sub>3</sub>=(CH<sub>2</sub>)<sub>4</sub>



d = -CO- insertion above NH<sub>2</sub> in each molecule

Figure 1b (Modified active molecule)

These active and modified molecules were docked into active site of PTP1B and docking score was evaluated. The molecules with improved docking score in comparison of active molecule as shown in Table2 were used for QSAR studies.

**Table2** Improved Molecules

Mol.No.	Improved Mol.	Docking Score
1.	1a(Active Mol.)	-98.584Kcal/mol
2.	[1b (a <sub>2</sub> , b <sub>1</sub> , c <sub>3</sub> , d)]	-130.261Kcal/mol
3.	[1b (a <sub>3</sub> , b <sub>2</sub> , c <sub>2</sub> , d)]	-130.596Kcal/mol
4.	[1b (a <sub>2</sub> , b <sub>2</sub> , c <sub>1</sub> , d)]	-131.740Kcal/mol
5.	[1b (a <sub>3</sub> , b <sub>2</sub> , c <sub>1</sub> , d)]	-122.297Kcal/mol
6.	[1b (a <sub>4</sub> , b <sub>2</sub> , c <sub>3</sub> , d)]	-126.602Kcal/mol
7.	[1b (a <sub>2</sub> , b <sub>3</sub> , c <sub>2</sub> , d)]	-121.306Kcal/mol

#### Calculation of molecular descriptors and regression

For calculation of molecular descriptors such as VerloopB1 (smallest width of substituent), VerloopB5 (maximum width of substituent), Total dipole moment(TDM), Dipole moment(DM), Bond dipole moment(BDM), log (lipophilicity), Total lipole (TL), Lipole, Bond lipole(BL), Molecular refractivity(MR), firstly the three substituents were defined from positions a, bc and d for all molecules. The calculation of molecular descriptors of oxalyl aryl amino benzoic acid derivatives as well as regression analysis were carried out using the molecular package TSAR 3D version 3.3 for windows<sup>9</sup>. The details of descriptors are available in molecular package guides and therefore they are not described here.

#### Results and Discussion

The success of QSAR studies mainly depends whether or not the molecular descriptors chosen are appropriate to explain biological activity. In our present study we have used VerloopB1, VerloopB5, Total dipole moment(TDM), Dipole moment(DM), Bond dipole moment(BDM), logP, Total lipole (TL), Lipole, Bond lipole(BL), Molecular refractivity(MR) as independent descriptors for all the three defined substituents. The compounds are divided into training and test sets each consisting of 13 and 6 molecules respectively. The training set is used for model development and test set is used for cross validation of QSAR model developed by training set. The calculated molecular descriptors are shown in Table3. The independent variables are correlated with antidiabetic activity of series of oxalyl aryl amino benzoic acid derivatives. The different monoparametric models and Classes developed on the basis of activity data by partial least square and discriminant analysis for antidiabetic activity of training and test molecules are presented in Table4. The most active training molecule i.e. first one found from literature falling into class 2 and test molecules are falling in better class, it means these can show better inhibition against PTP1B. Although some of training molecules are falling in class1 but these do not show selective inhibition against PTP1B found from literature<sup>12</sup>.

**Table3** Calculated molecular descriptors for the compounds

Com.	VerloopB1 (subst.1)	VerloopB1 (subst.2)	VerloopB1 (subst.3)	VerloopB5 (subst.1)	VerloopB5 (subst.2)	VerloopB5 (subst.3)	TDM (subst.1)	TDM (subst.2)	TDM (subst.3)
<b>Training Set</b>									
1.	1.942	1.55	1.65	7.7509	4.2982	3.1662	3.1358	2.4565	0.83426
2.	1.65	1.55	1.65	9.0979	4.2979	3.1652	3.2314	2.4191	0.84748
3.	1.9373	1.55	1.65	5.9409	4.3967	3.1643	2.8713	2.2836	0.40462
4.	1.65	1.55	1.65	9.6687	4.3899	3.1651	4.329	2.3746	03.36415
5.	1.9448	1.55	1.65	7.1191	4.3971	3.1652	4.325	2.2498	0.39835
6.	1.65	1.55	1.65	8.4914	4.3908	3.1654	3.5674	2.3456	0.37521
7.	1.65	1.55	1.65	8.5228	4.3956	3.1649	1.5171	2.3225	0.37119
8.	1.65	1.55	1.65	10.358	4.3919	3.1641	4.3854	2.3451	0.37102
9.	1.9537	1.55	1.65	6.9204	4.3961	3.1664	3.5603	2.2867	0.38615
10.	2.0128	1.55	1.65	9.2452	4.3952	3.1645	3.9515	2.3395	0.3744
11.	1.65	1.55	1.65	11.075	4.2863	3.1694	3.6106	2.473	0.44439
12.	1.9482	1.55	1.65	9.4614	4.3958	3.1637	3.4817	2.308	0.36497
13.	1.9252	1.55	1.65	7.7917	4.3953	3.1642	4.006	2.3013	0.38469
<b>Test Set</b>									
14.	2.0582	1.8406	1.65	7.2859	4.2779	2.0327	2.5545	0.4257	023481
15.	2.0864	1.7413	1.65	7.3585	4.2153	3.1825	2.621	0.70539	0.32611
16.	1.65	1.793	1.65	9.3065	4.2811	2.0296	2.9847	0.45231	0.23684
17.	1.65	1.673	1.65	9.3425	4.2728	3.169	2.9419	0.5044	0.5002
18.	1.65	1.7575	1.9258	8.7847	4.2112	3.1748	2.9612	0.69868	0.34984
19.	1.65	1.7208	1.65	8.5254	4.2671	2.0293	3.2621	0.48981	0.25241

Com.	DM(X) (subst.1)	DM(X) (subst.2)	DM(X) (subst.3)	DM(Y) (subst.1)	DM(Y) (subst.2)	DM(Y) (subst.3)	DM(Z) (subst.1)	DM(Z) (subst.2)	DM(Z) (subst.3)
<b>Training Set</b>									
1.	-1.1503	-2.1583	-0.39624	-2.5988	-0.53437	0.724	-1.3254	1.0442	0.12173
2.	-2.8044	-17496	0.49081	1.5495	-1.5501	-0.68915	0.41944	-0.62292	-0.049084
3.	2.2805	-1.7101	-0.010446	-1.6922	-0.52146	0.28499	0.42412	-1.4207	-0.28704
4.	2.1221	-1.8166	0.06053	-3.7335	-0.42425	0.23504	0.54554	-1.4693	-0.27147
5.	0.6496	-1.5719	-0.008608	-4.2582	-0.57538	0.33917	-0.38867	-1.5032	-0.20874
6.	-1.6019	-1.7111	0.024935	-3.1633	-0.66444	0.26238	0.39251	-1.4604	-0.26705
7.	-0.45891	-1.5819	0.041756	-0.8526	-0.64493	0.25694	-1.168	-1.5734	-0.26461
8.	-1.9223	-1.6596	0.025942	-3.768	-0.67375	0.25972	1.1567	-1.5137	-0.26369
9.	1.3773	-1.6743	-0.012872	-3.0148	-0.62606	0.29755	1.3	1.4261	-0.24579
10.	-0.54082	-1.7751	0.027811	-3.634	-0.77452	0.28188	1.4545	-1.3123	-0.24483
11.	-1.1521	-2.4331	0.015402	-2.5055	-0.047818	0.44294	-2.1148	0.44033	-0.032342
12.	-0.48813	-1.621	0.069345	-3.1291	-0.563044	0.2642	-1.4466	-1.5433	-0.24207
13.	-1.511	-1.7796	0.0070202	-3.4687	-0.63387	0.29027	1.3165	-1.3143	-0.25234
<b>Test Set</b>									
14.	0.80698	0.0361	0.19647	-2.3943	0.41749	0.12836	-0.37642	0.074958	-0.007516
15.	1.0077	0.317331	0.047998	-2.3063	0.57487	0.31999	-0.73161	0.25773	-0.040617
16.	0.71279	0.075307	0.1934	-2.5944	0.37907	0.13294	1.2921	0.23499	-0.031905
17.	0.61771	0.035524	-0.01119	-2.6229	0.34682	0.37625	1.1806	0.36452	0.32942
18.	0.43702	0.23247	0.13821	-2.1686	0.34756	0.31726	1.9685	0.12153	0.051269
19.	-2.6046	0.14127	0.18081	1.6108	0.37856	0.14834	-1.1239	0.27686	-0.094948

*Calicut Medical Journal 2008; 6(4): e3*

Com.	BDM (subst.1)	BDM (subst.2)	BDM (subst.3)	logP (subst.1)	logP (subst.2)	logP (subst.3)	TL (subst.1)	TL (subst.2)	TL (subst.3)
<b>Training set</b>									
1.	-3.5487	-2.9343	0.71269	-0.3434	-0.7067	1.0446	1.8033	1.4533	0.38501
2.	-1.2911	-2.8852	0.74539	1.6183	-0.7067	1.0446	6.6335	1.4531	0.38475
3.	1.6864	-2.2444	1.0815	0.4903	-0.7067	1.0446	7.4465	1.4775	0.38554
4.	-0.05073	-2.3391	1.1004	1.3551	-0.7067	1.0446	6.5581	1.4789	0.38584
5.	-0.94822	-2.1238	1.15	1.2256	-0.7067	1.0446	5.1264	1.4793	0.38498
6.	-2.7797	-2.3194	1.1246	0.937	-0.7067	1.0446	3.8804	1.4794	0.38591
7.	-1.2578	-2.2653	1.1212	-1.5632	-0.7067	1.0446	5.6447	1.4786	0.38543
8.	-3.1246	-2.3274	1.1345	-0.5641	-0.7067	-1.0446	2.2537	1.4786	0.38581
9.	0.2841	-2.2693	1.4465	0.9305	-0.7067	1.0446	5.6039	1.4776	0.38538
10.	-2.4576	-2.3714	1.109	-0.000899	-0.7067	1.0446	3.9301	1.4788	0.38609
11.	-3.4038	-2.5177	1.1413	-1.289	-0.7067	1.0446	2.0798	1.4809	0.3901
12.	-2.549	-2.2427	1.0911	-0.3117	-0.7067	1.0446	2.3071	1.4788	0.38618
13.	-3.009	-2.343	1.1371	-0.3434	-0.7067	1.0446	1.8368	1.4782	0.38577
<b>Test Set</b>									
14.	0.391	-0.89434	0.97592	-1.1147	-0.9872	0.6483	3.1719	1.3995	0.39247
15.	-0.61313	-1.2014	1.1421	-1.1147	-0.9872	1.0446	3.1575	1.378	0.39641
16.	0.67506	-0.88918	0.96001	-0.7397	-0.9872	0.6483	4.7134	1.3994	0.36287
17.	0.70779	-0.91167	1.2339	-0.7397	-0.9872	1.0446	4.7044	1.4016	0.38765
18.	0.67799	-1.2196	1.0276	-1.1822	-0.9872	1.3751	3.0787	1.3782	0.48942
19.	0.22225	-0.87714	0.9471	-0.9501	-0.9872	0.6483	3.3329	1.4002	0.36331

Com.	Lipole(X) (subst.1)	Lipole(X) (subst.2)	Lipole(X) (subst.3)	Lipole(Y) (subst.1)	Lipole(Y) (subst.2)	Lipole(Y) (subst.3)	Lipole(Z) (subst.1)	Lipole(Z) (subst.2)	Lipole(Z) (subst.3)
<b>Training Set</b>									
1.	0.11748	-095433	-021774	0.2599	-1.0814	0.31448	-1.7806	-0.17819	0.043823
2.	-3.7495	-1.3966	0.16418	5.3342	-0.264556	-0.34303	1.2213	0.30156	-0.058393
3.	6.7269	-028104	-0.33428	-3.1641	-1.2201	0.17774	0.43334	-0.78444	-0.072863
4.	4.7409	-0.47263	-0.28617	-4.0399	-1.2603	0.22603	-2.0521	-03.61276	-0.12604
5.	4.4961	-0.34014	-0.3361	-2.4277	-1.3054	0.18035	0.41364	-0.60703	-0.052141
6.	1.7271	-0.30349	0.31073	-3.3836	-1.7174	0.19513	0.79103	-0.60069	-0.11956
7.	-5.3476	-0.2628	-0.30127	1.3876	-1.3051	0.19791	1.1579	-0.6433	0.13648
8.	-1.683	-0.23679	-0.30999	1.0732	-1.2976	0.1874	1.0464	-0.66818	-0.13282
9.	5.1802	-0.24089	-0.33412	-1.9191	-1.2561	0.17558	-0.94148	-0.73983	-0.077793
10.	2.5118	-0.28615	-0.31571	-2.3684	-1.3073	0.19178	-1.8782	-0.62915	-0.11232
11.	-1.949	-0.79084	-0.34753	0.30028	-0.93123	0.17634	-0.6609	0.83702	-0.017527
12.	0.6318	-0.29767	-0.2903	-1.481	-1.2816	0.21261	-1.6523	-0.67513	-0.14018
13.	1.3571	-0.29091	-0.32404	-0.86294	-1.2504	0.18613	-0.88733	-0.73267	-0.095766
<b>Test Set</b>									
14.	2.173	0.35165	0.30973	-2.018	-1.3336	0.18512	-1.1255	-0.23778	-0.03439
15.	2.4968	0.30005	0.30634	-1.693	-1.3114	0.17671	-0.93237	-0.29867	-0.17909
16.	3.0311	0.41694	0.29683	-3.5034	-1.2649	0.1912	0.86849	-0.42941	-0.083816
17.	2.862	0.5639	-0.35451	-3.6491	-1.2597	0.13767	0.69631	-0.24407	0.075122
18.	2.1809	0.40696	0.36811	-1.8865	-1.1715	0.18793	1.0785	-0.60122	-0.26313
19.	-2.9875	0.51467	0.22159	1.1763	-1.2451	0.22866	0.89417	-0.38144	-0.17494

**Calicut Medical Journal 2008; 6(4): e3**

Com.	BL (subst.1)	BL (subst.2)	BL (subst.3)	MR (subst.1)	MR (subst.2)	MR (subst.3)
<b>Training Set</b>						
1.	-1.0612	-1.9174	2.4473	51.002	13.666	10.103
2.	7.7919	-1.9144	2.4486	52.456	13.666	10.103
3.	8.2304	-1.8564	2.4503	60.108	13.666	10.103
4.	6.253	-1.8662	2.4518	52.285	13.666	10.103
5.	10.873	-1.8389	2.4467	54.663	13.666	10.103
6.	4.3737	-1.8698	2.4517	47.263	13.666	10.103
7.	-10.906	-1.862	2.4494	46.279	13.666	10.103
8.	-3.2272	-1.87	2.4508	50.978	13.666	10.103
9.	10.141	-1.8574	2.4483	47.393	13.666	10.103
10.	0.8864	-1.8724	2.4525	55.75	13.666	10.103
11.	-5.3496	-1.8956	2.497	51.85	13.666	10.103
12.	2.1896	-1.8623	2.4537	55.771	13.666	10.103
13.	-1.0455	-1.8711	2.4507	51.002	13.666	10.103
<b>Test Set</b>						
14.	-2.4853	-2.401	1.504	35.677	18.607	5.5021
15.	-2.5618	-2.4396	2.5314	35.677	18.607	10.103
16.	0.25435	-2.3974	1.501	46.401	18.607	5.5021
17.	0.2554	-2.4033	2.4894	46.401	18.607	10.103
18.	-1.2828	-2.4425	3.3331	40.226	18.607	14.652
19.	0.37507	-2.4057	1.5017	39.702	18.607	5.5021

**Table4** Best QSAR models for antidiabetic activity of oxalyl aryl amino benzoic acid derivatives.

QSAR Model No.	QSAR Models	Predicted Classes
Training Molecules		
1.	-6.4136e+005	Class2
2.	-6.4075e+005	—
3.	-6.3722e+005	—
4.	-6.3811e+005	Class2
5.	-6.3839e+005	Class1
6.	-6.4287e+005	Class1
7.	-6.4324e+005	Class2
8.	-6.4137e+005	Class1
9.	-6.4282e+005	Class1
10.	-6.3929e+005	Class1
11.	-6.4101e+005	Class1
12.	-6.3928e+005	Class2
13.	-6.4136e+005	—
Test Molecules		
14.	-8.1742e + 005	Class1
15.	-9.7969e + 005	Class1
16.	-7.9541e + 005	Class1
17.	-9.4661e + 005	Class1
18.	-1.1706e + 005	Class1
19.	-7.6989e + 005	Class1

### Conclusions

The results and discussion made above lead to the conclusion that antidiabetic activity of series of oxalyl aryl amino benzoic acid derivatives can be successfully modeled using molecular descriptors. The designed molecules are coming in better class and it means these can show better selective inhibition against PTP1B. In our further studies these molecules will be recommended for organic synthesis for validation of docking and QSAR studies.

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