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Studies on two types of PTP1B inhibitors for the treatment of type 2 diabetes: Hologram QSAR for OBA and BBB analogues

Yuanhua Cheng [a], Mei Zhou [b], Chen-Ho Tung [a], Mingjuan Ji [b,*], Fushi Zhang [a,*]

[a] Key Laboratory of Organic Optoelectronics and Molecular Engineering of Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, PR China
[b] College of Chemistry and Chemical Engineering, Graduate University of Chinese Academy of Sciences, Beijing 100049, PR China

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ABSTRACT

Hologram quantitative structure–activity relationships (HQSAR) analysis were conducted on two series of PTP1B inhibitors, 39 2-(oxalylamino) benzoic acid (OBA) analogues and 60 benzofuran and benzothiophene biphenyls (BBB) analogues. The optimal HQSAR model of the OBA analogue has $q^2 = 0.592$ and $r^2 = 0.940$, while the optimal HQSAR model for the BBB analogues shows $q^2 = 0.667$ and $r^2 = 0.863$. Two models were employed to predict the biological activities of two test sets. For OBA analogues, the optimal model was validated by an external test set of six compounds with satisfactory predictive r^2 value of 0.786. For BBB analogues, the optimal model shows satisfactory predictive r^2 value of 0.866 for an external test set of 10 compounds. The contribution maps derived from the optimal HQSAR models are consistent with the biological activities of the studied compounds. Two virtual combinatorial libraries were designed and screened by the optimal HQSAR models and potential candidates with high predictive biological activities were discovered. This work may provide valuable information for future design of more promising inhibitors for PTP1B.

Protein tyrosine phosphatases (PTPs), a large family of signaling enzymes, serve as paramount regulatory components in numerous cell functions including growth, mitogenesis, motility, cell–cell interaction, metabolism, gene transcription, and immune responses.[1–3] In vivo, tyrosine phosphorylation is reversible and dynamic, with the phosphorylation states of proteins being governed by opposing actions of two enzyme families; protein tyrosine kinase (PTKs), which catalyze the formation of phosphotyrosyl residues in peptide and protein substrates, and the PTPs, which are responsible for dephosphorylation.[4] PTKs, PTPs and their associated substrates are integrated within signal transducing networks,[5] whose defective and unregulated operations give rise to many human diseases including cancer, diabetes and obesity.[6–8] Protein tyrosine phosphatases 1B (PTP1B) is a member of PTP family. It has been identified to play a major role in the dephosphorylation of insulin receptor (IR) and IR substrate thus abrogating insulin signaling.[9–11] Compelling data for this negative role of PTP1B were reported by two laboratories. PTP1B knockout studies in mice indicate that mice lacking PTP1B exhibit improved sensitivity to insulin and are resistant to high-fat diet induced obesity.[12,13] A recent study demonstrated that in vivo, the phosphorylation state of the Y1162/Y1163 site in the activation loop of the IR PTK catalytic domain is regulated by PTP1B.[14] Based on these studies, PTP1B-specific inhibitors might be expected to enhance insulin sensitivity and act as effective therapeutics for the treatment of type 2 diabetes and obesity. As a result, the design of novel PTP1B inhibitor has intrigued international passion in the last few years.[15–18]

HQSAR is a modern 2D-QSAR technique that eliminates the need of 3D structure determination, conformational search and molecular alignment.[19] Compared with the 3D-QSAR technique, such as CoMFA and CoMSIA, HQSAR could also easily and rapidly generate QSAR models with high predictive value for both small and large data set.[20] Besides, HQSAR models could interpret both positive and negative contributions based on various atoms and structural units, which are alternatives to 3D-QSAR models. Although several papers were published for the 3D-QSAR studies of PTP1B inhibitors, the HQSAR studies of these inhibitors have rarely been reported.[21,22] In this Letter, two HQSAR models were generated and evaluated using two series of PTP1B inhibitors, 39 OBA analogues and 60 BBB analogues.

These analogues were taken from previous works.[23,24] Chemical structures with experimental and predicted biological activity of OBA analogues and BBB analogue are listed in Table 1 and Table 2, respectively. The binding affinity pK_i ($-\log K_i$) (μM) for OBA and pIC_{50} ($-\log IC_{50}$) (μM) for BBB were used as dependent variables in HQSAR analyses. An essential characteristic of a training set is that the molecules must be orthogonal (i.e., dissimilar from each other). Surflex-Sim is able to provide the most orthogonal and diverse set of molecules to be included in the training set.[25]

* Corresponding authors. Tel.: +86 10 62782456; fax: + 86 10 62770304 (F.Z.), tel.: +86 10 88256326; fax: + 86 10 88256093 (M.J.).
E-mail addresses: jmj@gucas.ac.cn (M. Ji), zhangfs@mail.thu.edu.cn (F. Zhang).

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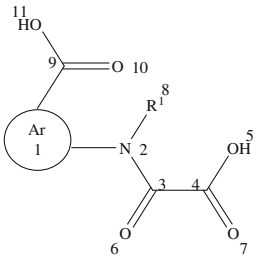
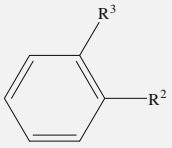
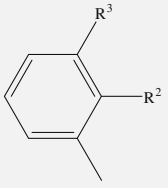
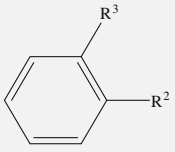
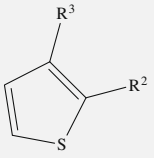
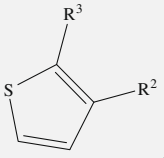
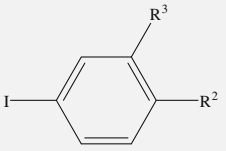
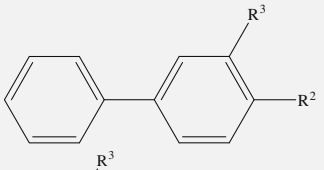
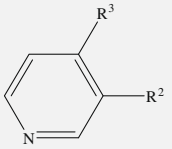
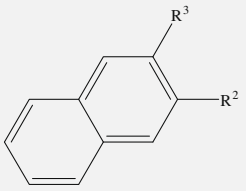
Table 1
Chemical structures, experimental and predicted activities, and residuals of training set and test set of OBA analogues



Compound	Ar[a]	R^1	Experimental	Predicted	Residual
1		H	4.64	4.40	0.24
2		H	2.9	2.83	0.07
3		Me	2.96	2.92	0.04
4		H	3.97	4.16	−0.19
5		H	4.43	4.31	0.12
6		H	4.85	4.73	0.12
7		H	4.85	5.15	−0.30
8		H	3.80	3.86	−0.06
9		H	5.00	5.12	−0.12