Chapter IV: Overall summary and Future prospects
4. Overall Summary and Future prospects

4.1 Overall summary of the present investigation

T2DM is a complex multifactorial disease affecting quality of life of an affected individual. T2DM is a progressive disorder accompanied by deterioration in β cell function and insulin resistance. Despite this fact, there is now clear evidence that tight control of blood glucose significantly reduces the risk of complications of diabetes. PTP-1B inhibitors, which control the activity of PTP 1B, known as negative regulator of insulin signaling offers safe and effective mean for treating metabolic diseases.

In last few decades, several small molecules based-PTP-1B inhibitors are reported in the literature, however, no PTP-1B inhibitor has reached to the market, mainly due to their lack of selectivity over TC-PTP and poor oral bioavailability.

For my PhD dissertation work, altogether three series of PTP-1B inhibitors were designed. In the first series, as benzotriazole based PTP-1B inhibitors, total fifteen compounds were prepared. In the second series, based on triaryl-sulfonamide derivatives as PTP-1B inhibitors, total nineteen compounds were prepared. In the third series, total twenty three peptidomimetics derivatives were prepared as PTP-1B inhibitors. Altogether fifty-seven compounds were synthesized, purified, characterized and were subjected to in vitro PTP-1B inhibitory activity. The most potent selected PTP-1B inhibitors from each series were further subjected to the in vitro selectivity over other PTPs (especially over TC-PTP). From each series, the most potent and selective compounds were subjected to the in vivo antidiabetic
activity including PK studies. All the three series were found to be potent and selective PTP-1B inhibitors.

In the first series, test compounds 13a and 13c showed excellent PTP-1B inhibition (*in vitro*) along with selectivity over PTPs, therefore 13a and 13c were considered as optimized lead from this series.

*In vivo* and *in vitro* PTP-1B inhibitory activity and molecular docking studies results of 13a and 13c clearly demonstrated that the potency and selectivity of benzotriazole based PTP-1B inhibitors can be modulated using suitable introduction of pyTyr mimetic. Furthermore, it was observed that suitable introduction of pyTyr mimetics on benzotriazole scaffold contributed significantly towards improvement in the *in vivo* PTP-1B inhibitory activity, which could be correlated with the improved oral bioavailability. The *in vitro* and *in vivo* studies, results of 13a demonstrated potent *in vitro* PTP-1B inhibitory activity and more than 100-fold selectivity against TC-PTP. In PK studies, compound 13a showed good oral bioavailability, indicating that the test compound 13a is a promising candidate for safe and effective treatment of T2DM and need to subject to further pre-clinical evaluation.

In the second series, our attempt to replace pyTyr mimetic of compound V with its more potent pyTyr mimetics, lead to the development of novel, potent, selective and structurally diverse scaffold as PTP-1B inhibitors. Most potent compound 54e from this series showed nM potency (PTP-1B inhibitory activity), which was found to be better than V. It also showed improvement in the fold selectivity over various PTPs. Thus, preliminary PK studies results reveal that a further modification on 54e may lead to the
identification of a potent compound from this series, with improved bioavailability for the efficient treatment of T2DM.

In the third series, modification of peptidomimetic derivatives of IX (preliminary hit) was carried out by suitable changes at C and N terminals of compound IX, and we identified progressive lead compounds 67c and 67d, which showed PTP-1B inhibitory activity in nM range with more than 95-fold selectivity over TC-PTP.

Table. 14 Short listed key compounds from 3 different series

<table>
<thead>
<tr>
<th>Series</th>
<th>Structure</th>
<th>In vitro (PTP-1B) IC_{50} nM</th>
<th>In vitro (TC-PTP) IC_{50} nM</th>
<th>Fold Selectivity</th>
<th>PK ( \text{\mu g/mL}^{-1} )</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td><img src="image" alt="Structure 13a" /></td>
<td>5</td>
<td>580</td>
<td>116</td>
<td>10.562</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 54e" /></td>
<td>9</td>
<td>870</td>
<td>96</td>
<td>8.91</td>
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<tr>
<td></td>
<td>3</td>
<td>67c</td>
<td>0.13</td>
<td>14.22</td>
<td>110</td>
</tr>
<tr>
<td>---</td>
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<td>-----</td>
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<td>-------</td>
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<tr>
<td></td>
<td></td>
<td>67d</td>
<td>0.15</td>
<td>14.61</td>
<td>97</td>
</tr>
</tbody>
</table>

Compared to the previous two series, compounds 67c and 67d were not subjected to further in vivo evaluation, due to their metabolic instability and oral PK issues. However compounds 67c and 67d can be considered as primary lead from this series, which can be converted into clinical candidates by improving metabolic stability and oral PK. This series expands further scope for studying suitable structural modifications to treat T2DM. The key compounds of each series are listed in Table 14.

4.2 Future Prospects

From the first series, compound 13a showed excellent PTP-1B inhibitory activity (in vitro) & antidiabetic activity (in vivo). The PK profile of 13a was found to be satisfactory compared to the standard compound and therefore 13a represents a promising candidate to work on. Future work includes same additional safety study and pre-clinical studies before it can be subjected to clinical development. Compound 13a should be considered for chronic efficacy studies and for long term toxicological evolution, along with its PK profile in higher animals such as dog or monkey.
In the second series, compound 54e showed better *in vitro* PTP-1B inhibitory activity due to its strong interaction with site A and showed more than 90-fold selectivity over TC-PTP due to its strong interaction with site B, which was not observed in V. This discovery encourages us to move one step further ahead in designing potent and PTP-1B-specific inhibitors, which demands further structural modification. Compounds XIII & XIV are proposed modification in 54e, expected to improve its PTP-1B inhibitory activity, selectivity over TC-PTP and may result in a better PK profile (Figure 36).

*Figure 36. Future plans for series 2 modification*

In case of the third series, compound 67c was found to be most active among all the three series, but oral bioavailability was a major issue in the development of peptidomimetic based PTP-1B inhibitors. Thus, we may need to improve metabolic stability to achieve good oral bioavailability by oral route.
For this, the following future modifications in 67c are proposed to improve its 
*ex vivo* and *in vivo* activities along with its PK profile (*Figure 37*). Bioisosteric 
replacement of central amino acid (Aspartic acid) with unnatural amino acid 
(XV) or with spacer [(−CH₂)ₓ] (XVI), may improve its *ex-vivo* stability to over 
come oral bioavailability.

*Figure 37. Future plans for series 3 modifications*