4.1. INTRODUCTION

Diabetes is diagnosed by the presence of excess sugar (glucose) level in the blood than prescribed. The hormone named insulin in sufficient amount is needed by the body which is necessary for the uptake of glucose from the blood and transfer it to the cells to be used up by the cells of the body and use it in the form of energy. Insulin is secreted in the pancreatic gland of the body by beta cells. The diabetic symptoms include excessive thirst, excessive urination, slow wound healing and fatigue. The additional symptoms may include rapid weight loss, blurred vision, erectile dysfunction and numbness of hand and/or feet. Sometimes people although having diabetes may not experience symptoms and thus they become indefinite until having a blood sugar test.

On the basis of reported diabetic conditions, diabetes can be grouped into three major classes viz. Type 1, Type 2 and gestational diabetes. Type 1 Diabetic conditions are those in which the insulin secreting cells of pancreatic glands of the body gets damaged by the immune system of body itself, thus disabling the glucose uptake from blood and resulted into increased blood-sugar levels. Treatment of Type 1 diabetes preferably includes the regular injections of insulin. Type 2 Diabetes is diagnosed by the insufficient secretion of insulin by the pancreatic beta cells to transact glucose from the food taken. This usually occur in the people with middle to older age group, but now a days this type of diabetic disorder is more commonly occurring in younger age group due to their lifestyle. During pregnancy some women suffer from high blood glucose levels this condition is termed as gestational diabetes which disappears after birth. This might be due
to the insufficient insulin production by beta cells as required by the foetus containing body.

For the treatment of any type of diabetic disorder yet no drug is available. However medications are available for keeping the blood sugar level in control. These remedies are being designed to help the body in regulating the glucose level in blood\(^\text{3}\). The key to avoiding diabetic conditions is to keep good control over blood sugar by adding healthy lifestyle and proper medications.

In case of Type 1 diabetes the injected insulin compensated the lacking insulin in the body. While Type 2 diabetic treatment varies according to the blood sugar level. The important thing in this type of diabetes is to consult with a diabetic instructor and dietician because many of the sufferers have been advised to lose their weight and change life style. In such cases, the treatment starts with body workout and food change.

### 4.1.1. Major targeted sites of drug classes

Sulfonyl ureas act through ATP-dependent K\(^+\) channels, which results in an increased positive potential hence more insulin is needed. First Generation Drugs: Acetohexamide, tolbutamide, tolazamide, Second Generation Drugs: Glipizide, gliclazide, Third Generation Drugs: Glimepiride. Biguanides are from a natural source and suppress hepatic gluconeogenesis. Eg: Metformin, Phenformin. Alpha-glucosidase inhibitors competitively inhibit carbohydrate digesting enzymes and decrease postprandial hyperglycemia. Eg: Acarbose, Miglitol, Voglibose. Thiazolidinones work by activating PPAR-\(\gamma\) and cause increased release of insulin from fat and skeletal muscle tissue.
Eg: Rosiglitazone, Pioglitazone, Troglitazone. Glucagon-like peptide-1 (GLP-1) analogues act by enhancement of postprandial insulin release. Eg: Exenatide. DPP-IV inhibitors limit postprandial hyperglycemia by preventing the degradation of endogenous GLP-1 and other incretins. Eg: Sitagliptin.

### 4.1.2. Non pharmacological management

The cornerstone of treatment of diabetes is life style modification through increased physical activity and attention to food intake, particularly among the obese in which weight loss is the principal goal.

Diabetes is becoming an epidemic disease not only in developed countries but also steeping out widely in developing countries. World Health Organisation (WHO) has predicted of about 300 million people worldwide to be diagnosed by diabetes till 2025 if current lifestyle trends continues. Thus one cannot underestimate the need for the development of new alternative remedies for the treatment of this disease. In spite of the fact that the factors causing diabetes are not very clearly traced but seems to be multifactorial among which insulin resistance is thought to be the causal factor in the development of disease. It is relevant that a long time is needed to eradicate or reverse this physiological condition. Many diabetes therapies have been found to be effective that also include thiazolidinediones class for PPAR-γ receptor agonist and act as insulin sensitizer. Another target class tremendously attracting medicinal chemist for the treatment and prevention of diabetes is the development of drugs to inhibit enzyme protein tyrosine kinase-1B (PTP-1B).
PTP-1B is a non-transmembrane enzyme found on the endoplasmic reticulum, which is a negative regulator of insulin and leptin signalling\(^5\). The enzyme Protein Tyrosine Phosphatase 1B dephosphorylates the insulin receptor, and also from its primary substrate, by the removal of phosphate group from it. PTP1B also removes phosphate from the Janus kinase 2 (JAK2), a tyrosine kinase.

As yet researchers have not thought for PTP 1B as being the suppressor of tumor but now some clues have been found as it may serve as negative cell growth regulator\(^6\). Since PTP1B act as downregulator of receptor kinase still the knockout PTP1B mice have not been reported to develop tumors. Additionally overexpression of this enzyme was noticed in human cancers. Researchers worked out to establish the prooncogenic functions of PTP-1B in breast cancer.\(^7\) PTP1B can also open the doors for treating cancers by decreasing Ras signaling and inhibiting proliferation via newly identified mechanism.\(^8\) PTP 1B inhibition could also reduce colon cancer cell oncogenesis and this potential can lead these enzymes to be used as chemotherapeutics in colon and breast cancers.\(^9\)

The intracellular moiety of insulin receptor is a kinase which is activated by auto phosphorylation following interaction of the extracellular part with insulin. This is the first step of a cascade leading to glucose uptake through glucose transporter GLUT4\(^10\). The cascade is terminated by the dephosphorylation of the intracellular moiety of insulin receptor by PTP1B. Thus, PTP1B inhibition, resulting in prolonged maintenance of the phosphorylated state, practically enhances insulin effect\(^11\) and play as negative regulation in leptin receptor signalling pathway\(^12\).
A large number of PTP1B inhibitors have been found, the race for finding novel highly effective and selective inhibitors still continues.

4.2. BASIS OF WORK

Studies shown that inhibitors of PTP 1B enzyme put forward the new line of treatment for type II diabetes and obesity as well as might open doors for new anticancer agents. Many studies have been carried out showing PTP 1B as a factor for tumorogenesis. Thus molecules which inhibit these enzymes are becoming the attractive pharmaceutical agent for the treatment of Type II diabetes, obesity and cancer. A lot of studies have done over the past decade to develop the PTP 1B inhibitors for becoming the plausible drug candidates.

Figure 4.1: various types of PTP 1B inhibitors and our designed prototype
A careful survey of literature we found that the compounds in which the substituted biphenyl scaffold\textsuperscript{14-16} and thiazolidinedione\textsuperscript{17-20} moiety (figure 4.1) were found to be effective in treating Diabetic condition through PTP-1B inhibition mechanism.

Most of the previously reported molecules shown great potency in in vitro studies up to the nanomolar concentrations, but at the same these molecules also suffered from poor bioavailability and low cell permeability. Some of them were having poor pharmacokinetic and poor pharmacodynamic properties and causing severe toxicity due to biphenyl moiety. Thus for medicinal chemists probing the drug like properties in PTP1B inhibitors still represent a challenge. so our aim was to substitute this biphenyl moiety to other heterocyclic moiety so that the formed compounds having better ADME profiles (Absorption, Distribution, Metabolism, and Excretion) as well as devoid of liver toxicity and due structurally similar moiety with PPAR-\(\gamma\) agonist (Pioglitazone/ Rosiglitazone), we also tried to make compound which are also having PPAR-\(\gamma\) agonist activity along with PTP-1B Inhibition activity.

4.3. MATERIALS AND METHODS

4.3.1. Synthesis of basic pharmacophore and compounds

For the synthesis of thiazolidinedione derivative (3), we have reacted 4-hydroxybenzaldehyde (1) with Thiazolidine-2, 4-dione (2) via cross aldol condensation in the presence of piperidine base. (Scheme 4.1).
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Scheme 4.1: reagent and conditions: a) Toluene, piperidine, benzoic acid, 80 °C, refluxed, 8hrs

Scheme 4.2: Reagents and conditions: a) DMF, K₂CO₃, 140 °C, refluxed, 12 hr; b) DMF, K₂CO₃, 140 °C, refluxed, 2 hr; c) DMF, K₂CO₃, 140 °C, refluxed, 15 hr; d) Xylene, K₂PO₄, 80 °C, refluxed, 5 hr; e) Acetone, K₂CO₃, propargyl bromide (2.2 eq), Room Temp., overnight.

After synthesizing this basic pharmacophore (compound 3), we used it as our starting material. By the use of this starting compound we have synthesized six new compounds (4-9) as shown in Scheme 2. First we have reacted compound 3 with different reactants (4-chloro-2-
methylquinoline, 4,7-dichloroquinoline and 4-bromopyridine) and potassium carbonate in DMF at reflux for different periods of time to get compound 4, 5 and 6 respectively. Whereas the reaction of compound 3 with 3-bromopyridine was carried out by refluxing in xylene for 5h using $K_3PO_4$ as base which yielded into compound 7. Compound 8 and 9 were synthesized by reaction with propargyl bromide at different reaction conditions as shown in scheme 2.

4.4. RESULTS AND DISCUSSION

4.4.1. ANTIDIABETIC ASSAY

4.4.1.1. Enzymatic assay for compound screening

PTP-1B Assay Protein Tyrosine Phosphatase 1B (PTP 1B) is an enzyme that belongs to family tyrosine phosphatase. The PTPs family consist of a large group of enzyme (>100 in human) which participate in different signaling pathways that are important for the regulation of cell proliferation, differentiation, metabolism, migration and survival. In humans it is encoded by PTPIB is the prototype for the super family of PTPs and has been most extensively studied within the group. PTPIB was initially characterized as inhibitors of growth factor pathways, in particular insulin signaling. Transgenic overexpression of PTPIB in muscles causes insulin resistance in mice, whereas inhibition of these phosphatases enhances insulin signalling. The PTPIB is a biologically limiting regulator only for insulin and leptin signalling, but not for other pathways. Hence specific inhibition
of PTPIB could affect two essential features of the metabolic syndrome—insulin resistance and obesity—making it an exciting target for potential drug discovery. PTPIB inhibitors have been extensively reviewed during last several years.21

4.4.1.2. SIGNIFICANCE

If a compound found to be potent inhibitor of the PTP 1B enzyme than its effect will lead to increased insulin sensitivity to the Type 2 Diabetes pathophysiological condition.

4.4.1.3. Method

Compound synthesized has taken in 1mM (10 μl) concentration followed by addition of the 75 μl Assay buffer (0.5M HEPES, 10mM DTT, 20mM EDTA) to the incubation with the enzyme in quantity of 5 μl enzyme (0.5 to 0.6 U). After this 10 μl of substrate solution {PNPP (0.0M)} have been added and leave at 37 °C for 30 min. Reaction was left for some time to occur. Reaction was stopped by adding 50 μl of 0.1 N NaOH to read the Optical Density at 405 nm [Table 4.1].

**Enzyme** – PTP 1B either liver homogenate or recombinant  
**Substrate** – Standard inhibitor – Suramin

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Concentration</th>
<th>PTP-1B Inhibition (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>10 μM</td>
<td>-9.5</td>
</tr>
</tbody>
</table>
4.4.2. CYTOTOXICITY ASSAY

4.4.2.1. Preparation of test sample solutions

The test samples / molecules were weighed in microcentrifuge tubes and stock solutions of 20 mM were made by dissolving the samples in DMSO. Stocks were stored at -20 °C. A working solution of 20 µM concentration was made by diluting the stock solution in culture medium (RPMI-1640 with 5 % FBS) prior to the assay.

4.4.2.2. SRB Assay (sulfurhodamine B assay)

Addition of cells - The human cancer cell lines colon (DLD-1) and breast (MCF-7) were maintained in RPMI -1640 medium; breast (MDAMB-231) and colon (SW620) were maintained in DMEM medium. The innumerate cells were dispensed in a 96-well tissue culture plate. Each well receives 100 µl of the cell suspension containing 10,000-30,000 cells (depending upon the nature of cell line). The cells were then

<table>
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<tr>
<th></th>
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<th>10 µM</th>
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<tbody>
<tr>
<td>2</td>
<td>5</td>
<td>-7.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>-7.6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
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<td>5</td>
<td>8</td>
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</tr>
<tr>
<td>6</td>
<td>9</td>
<td>-24.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Suramin (std)</td>
<td>-36.5</td>
<td></td>
</tr>
</tbody>
</table>

20 µM

Suramin (std)
incubated at 37 °C in 5% CO₂ concentration for 24 hr before addition of the test samples/standard drugs.

**Addition of test samples** - 100 µl of working solutions of the test sample was added to the cell monolayer to give a final concentration 10 µM. for each sample, duplicate wells were included.

**Positive drug and negative (vehicle) controls** - In every assay plate both positive and vehicle controls were included. In positive control well, Adriamycin (Doxorubicin) was added at 10 µM concentration. In vehicle control wells, DMSO was added. In all assay wells the final concentration of DMSO was 0.1%. The plates were then incubated at 37 °C in 5% CO₂ concentration for 48 hr.

**Addition of SRB and Colorimetric reading** - After 48 hr incubation, cells attached to substratum of the plate were fixed by adding cold 50% trichoroacetic acid (TCA, 50 µl/well) on top of the medium and incubated at 4° C for 1 hr. after that the plate was gently washed 5 times with slow running tap water via plastic tubing to remove TCA, culture medium and dead cells. After washing the plates were allowed to dry in air. To the dry plates 50 µl/well of SRB solution was added and left at room temp for 30 min. then unbound SRB was remove by quickly rinsing plates 4-5 times with 1% (v/v) acetic acid. Plates were allowed to air dry at room temp. 150 µl of 10 mM Tris base solution was added to each well and plate was shaken for 15 min on a gyratory shaker to solubilise the protein-bound dye.
Absorbance was measured at 510 nm in a micro plate spectrophotometer.

**Selection Criteria** - During initial screening, the samples showing equal to or more than 80% growth inhibition of cancer cells at 10 µM concentration are considered as ‘Hits’.

Table 4.2: In-vitro cytotoxicity assay of synthesized compounds

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Comp.</th>
<th>DLD-1</th>
<th>SW620</th>
<th>MCF-7</th>
<th>MDAMB-231</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
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<td>9.3</td>
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<tr>
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<td>18.8</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>15.3</td>
<td>20.5</td>
<td>18.9</td>
<td>21.5</td>
</tr>
<tr>
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<td>8</td>
<td>10.0</td>
<td>15.8</td>
<td>13.4</td>
<td>18.7</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>9.4</td>
<td>17.6</td>
<td>15.5</td>
<td>20.0</td>
</tr>
</tbody>
</table>

**IC₅₀** values are given in µM concentration.

### 4.5. EXPERIMENTAL DETAILS WITH SPECTRAL AND ANALYSIS DATA

1. All reactions were monitored by TLC over silica gel plate. The spots on TLC plates were visualized under UV lamp or by iodine vapours.
2. Column chromatography was performed using silica gel as stationary phase and EtOAc and Hexane as eluent.
3. IR spectra were recorded using Perkin-Elmer’s Spectrum RX I FTIR spectrophotometer as KBr disc or neat as applicable.

4. $^1$H-NMR, and $^{13}$C-NMR spectra were recorded on Bruker Avance DPX-400 MHz, Avance DPX-300 MHz or Avance DPX-200 MHz FT Bruker spectrometers, using deuteriated solvents and TMS as an internal standard (as applicable). Data expresses the chemical shift values in $\delta$ ppm from downfield to upfield in both $^1$H-NMR and $^{13}$C-NMR spectra. For all compounds, $^1$H-NMR data is reported in the following order: Chemical shift (multiplicity, $J$ value, number of protons).

5. ES mass spectra were recorded in Merck M-8000 LCMS system or Micromass Quadro LCMS system and HR/EI mass were done on JEOL-600H at 70eV.

6. Elemental analyses were carried out on Carlo-Erba-1108 instrument or Elementar’s Vario EL III micro-analysers.

**General Procedure for the synthesis of 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (3)**

Into a round bottom flask (100 ml) equipped with magnetic bar was added 4-hydroxybenzaldehyde (1.0 mmol) and Thiazolidine-2,4-dione (1.0 mmol) in the presence of toluene as a solvent and stirred at room temperature for 45 min, after that added small amount of piperidine and heated the reaction mixture for 8hrs, after completion of the reaction as monitored by TLC, cooled the reaction mixture then added little amount of methanol and filtered off the product, a yellow colour solid is obtained. Yield- (98%) pale yellow.
solid, mp= 268-270 °C.; IR (KBr) ν$_{\text{max}}$ 3404, 1602, $^1$H NMR (DMSO-d$_6$, 400MHz) δ= 7.68 (s, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 8.7$ Hz, 2H); $^{13}$C NMR (DMSO-d$_6$, 101 MHz) δ= 168.6, 168.1, 160.0, 132.9, 132.3, 124.3, 119.2, 116.5. ESI-MS: (m/z) 222 (M+H)$^+$, Elemental Analysis calculated for C$_{10}$H$_7$NO$_3$S: C, 54.29; H, 3.19; N, 6.33; found: C, 54.27; H, 3.21; N, 6.30.

**Synthesis of quinoline compounds (4 & 5)**

Compound 3 (1.0 mmol) and potassium carbonate (3.0 mmol) were taken in round bottom flask; dissolved the compound in minimum amount of DMF. After that for the synthesis of compound 4 added 1.0 mmol of 2-methyl-4-chloroquinoline and for the synthesis of compound 5 we added 1.7 mmol of 4, 7-dichloro quinoline in the reaction mixture. The reaction mixture was refluxed at 140 °C for 12 hr & 2 hr respectively. After completion the reactions compound 4 was extracted with ethylacetate and washed with water, combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. Crude product was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/hexane as eluent. A light yellow coloured compound was obtained in excellent yield.

5-(4-(2-methylquinolin-4yloxy)benzylidene)thiazolidine-2,4-dione (4).

Yield- (80%) light yellow solid, mp= 248-253 °C. IR (KBr) ν$_{\text{max}}$ 3407, 1623, 1680. $^1$H NMR (CDCl$_3$, 400MHz) δ = 8.54 (d, $J = 5.2$ Hz, 1H), 8.09 (d, $J = 8.9$ Hz, 1H), 7.90 (s, 1H), 7.61(s, 1H), 7.44(d, $J= 8.5$ Hz,
2H), 7.38 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.50 (d, J = 5.1 Hz, 1H), 2.5 (s, 3H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ = 167.1, 164.3, 160.8, 159.2, 157.7, 145.2, 131.2, 129.8, 129.2, 128.9, 127.3, 123.9, 123.6, 120.1, 119.8, 115.4, 109.5, 24.3; ESI-MS: (m/z) 363(M+H)$^+$.

For compound 5, after completion of reaction we added toluene and methanol in the reaction mixture and leave it for a while, after 2 days a precipitate was settled down on the bottom which was filtered and washed with methanol (2X). Off-white coloured solid was obtained with good yield.

5-(4-(7-chloroquinolin-4yloxy)benzylidene)thiazolidine-2,4-dione (5)

Yield- (90%); off-white solid, mp= 255-260 $^\circ$C. IR (KBr) $\nu$$_{max}$ 341, 1614, cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400MHz) $\delta$ = 8.54 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 8.9 Hz, 1H), 7.90 (s, 1H), 7.61 (s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.38 (d, J= 8.9Hz, 1H), 7.11 (d, J= 8.5Hz, 2H), 6.50 (d, J= 5.1 Hz, 1H), $^{13}$C NMR (CDCl$_3$, 101MHz) $\delta$ = 167.1, 159.3, 158.3, 157.7, 151.0, 146.3, 135.3, 129.8, 129.3, 127.3, 126.5, 125.9, 124.1, 120.2, 119.8, 119.2, 105.9; ESI-MS: (m/z) 383(M+H)$^+$. Elemental Analysis calculated for C$_{19}$H$_{11}$ClN$_2$O$_3$S: C, 59.61; H, 2.90; N, 7.32, found: C, 59.65; H, 2.92; N, 7.36.
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Synthesis of pyridine compounds (6 & 7)

**Compound 3** (1.0 mmol) and potassium carbonate (3.0 mmol) were taken in round bottom flask and dissolved in minimum amount of DMF. After that 4-bromopyridine (1.0 mmol) and 3-bromopyridine (1.0 mmol) respectively for the synthesis of compound 6 & 7, were added in the round bottom flask. The reaction mixture was reflux at 140 °C for 15hr. After completion the reaction, the mixture was extracted with ethylacetate and water, the combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. Crude product was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/hexane as eluent. Dark yellow coloured compounds were obtained in appreciable yield.

**5-(4-(pyridin-4-yloxy)benzylidene)thiazolidine-2,4-dione (6)**

![Structure.png](attachment:Structure.png)  
Yield- (75%) Dark yellow solid, mp- 268-273 °C. IR (KBr) ν_{max} 3402, 1626, ¹H NMR (DMSO-d₆, 400MHz) δ =10.26 (s, 1H), 7.63 (s, 1H), 7.44 (d, J= 8.7 Hz, 4H), 6.91 (d, J= 8.6 Hz, 4H); ¹³C NMR (DMSO-d₆, 101MHz) δ = 169.0, 168.8, 159.9, 150.7, 132.5, 132.1, 131.9, 129.9, 124.6, 120.8, 119.6, 115.8, 112.7; ESI-MS: (m/z) 299 (M+H)⁺, Elemental Analysis calculated for C₁₅H₁₀N₂O₃S: C, 60.39; H, 3.38; N, 9.39, found: C, 60.42; H, 3.40; N, 9.36.

**5-(4-(pyridin-3-yloxy)benzylidene)thiazolidine-2,4-dione (7)**

Yield- (60%) yellow solid, mp-260-265 °C. ¹H NMR (CD₃OD, 400MHz) δ = 7.77 (s, 2H), 7.45 (d, J= 8.6 Hz, 4H), 6.92 (d, J= 8.7 Hz,
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4H); $^{13}$C NMR (CD$_3$OD, 101 MHz) $\delta$ = 167.1, 159.3, 157.6, 152.7, 146.2, 138.9, 130.1, 129.1, 127.3, 125.7, 124.6, 120.1, 119.8. ESI-MS: (m/z) 299 (M+H)$^+$, Elemental Analysis calculated for C$_{15}$H$_{10}$N$_2$O$_3$S: C, 60.39; H, 3.38; N, 9.39, found: C, 60.41; H, 3.40; N, 9.44.

**Synthesis of compounds (8 & 9)**

Compound 3 (1.0 mmol) and K$_3$PO$_4$ (10.0 mmol) were taken in round bottom flask. For the synthesis of compound 8, 1.2 mmol of propargyl bromide was added to the reaction mixture and dissolved in 10 ml of xylene. The reaction mixture was refluxed at 80 °C for 5 hr. after completion the reaction, the reaction mixture was extracted with ethyl acetate and washed with water. The combined organic layers were dried over anhydrous sodium sulphate and concentrate in vacuo. A dark yellow coloured compound was obtained in excellent yield.

5-(4-(prop-2-ynyloxy)benzylidene)thiazolidine-2,4-dione (8)

Yield- (60%) yellow solid, mp= 155-160 °C. $^1$H NMR (CDCl$_3$, 400MHz) $\delta$ = 8.03 (s, 1H), 7.63 (d, $J$= 8.7 Hz, 2H), 7.20 (d, $J$= 1.8 Hz, 2H), 4.89 (d, $J$= 3.6 Hz, 2H), 2.70 (s, 1H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ = 167.1, 161.4, 159.3, 130.1, 127.3, 125.5, 120.2, 115.9, 80.0, 78.8, 58.8; ESI-MS: (m/z) 260 (M+H)$^+$, Elemental Analysis calculated for C$_{13}$H$_9$NO$_3$S: C, 60.22; H, 3.50; N, 5.40, found: C, 60.18; H, 3.48; N, 5.43.
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Compound 3 (1.0 mmol), potassium carbonate (10.0 mmol), propargyl bromide (2.2 mmol) and dry acetone (10 ml) were taken into the round bottom flask for the synthesis of compound 9. The reaction mixture was stirred at room temperature for overnight, after completion of the reaction; the reaction mixture was extracted with ethyl acetate and washed with water. The combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. Crude product was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/hexane as eluent. A light yellow coloured compound was obtained in appreciable yield.

5-(4-(prop-2ynyloxy)benzylidene)-3-(prop-2yny)thiazolidine-2,4-dione (9)

Yield- (95%) light yellow solid, mp- 170-175 °C. IR (KBr) ν\text{max} = 3412, 1739, 1688, \text{H NMR} (CDCl}_3, 400MHz) δ = 7.92 (s, 1H), 7.52 (d, J= 8.7 Hz, 2H), 7.11 (d, J= 8.8 Hz, 2H), 4.78 (d, J= 2.4 Hz, 2H), 4.52 (d, J= 2.5 Hz, 2H), 2.59 (t, J= 2.4 Hz, 1H), 2.29 (t, J= 2.5 Hz, 1H); \text{C NMR} (CDCl}_3, 101MHz) δ = 166.9, 165.2, 159.4, 134.3, 132.3, 126.5, 118.4, 115.7, 77.7, 76.3, 76.1, 72.1, 55.9, 30.6, 29.7; ESI-MS: (m/z) 298 (M+H)+, Elemental Analysis calculated for C\text{16}H\text{11}NO\text{3}S: C, 64.63; H, 3.73; N, 4.71, found: C, 64.66; H, 3.75; N, 4.75.

4.6. CONCLUSION

The intracellular enzyme PTP 1 B acts as a negative regulator of leptin and insulin signaling pathways. This is achieved by catalyzing the dephosphorylation of specific phosphotyrosineB (pTyr) residues on
insulin receptor, insulin receptor substrate proteins and on Janus kinase 2, a protein tyrosine kinase which is associated with leptin receptors. Inhibition of PTP 1B results in both increased insulin sensitivity and resistance to obesity. This makes PTP 1B an exemplary target for obesity and type 2 diabetes (DM2).

Till date various PTP–1B inhibitors are reported, we have done structural modification in existing PTP–1B inhibitor for improving its ADME Properties. So we synthesized total 6 compounds were synthesized and given for PTP-1B inhibitory activity as well as anticancer activity. Out of the screened compounds 5-(4-(prop-2-ynyloxy)benzylidene)-3-(prop-2-ynyl)thiazolidine-2,4-dione (9) was found to be active against PTPb (–24.5% PTP inhibition) and 5-(4-(7-chloroquinolin-4yloxy)benzylidene)thiazolidine-2,4-dione (5) has been found to show activity against MDAMB-231 cell line as anticancer agent.
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4.7. REFERENCES

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1^H NMR Spectra of Compound 3
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13C NMR Spectra of Compound 3

1H NMR Spectra of Compound 9
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