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Co-crystallized ligand based designing and synthesis of some heterocyclic derivatives of chalcone as "protein-tyrosine phosphatase 1B" inhibitors

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Protein tyrosine phosphatase 1B (PTP1B) is an important target for diabetes since inhibition of PTP1B offers therapeutic benefits in insulin resistant diabetes. Unfortunately, no drugs are approved or available in market as PTP1B inhibitor and finding of such type of anti-diabetic agents is still in progress. However, computational modeling, based on the interaction between co-crystallized ligand and macromolecular receptor has presented some structural features required for PTPIB inhibitory activity. Considering these structural features of co-crystallized ligand bound with 3D crystal structure of PTP1B receptor we have designed some chalcones and their heterocyclic derivatives as PTP1B inhibitors. Preliminary substituted chalcones have been investigated but only one phenyl ring of these derivatives shows interaction with PTP1B receptor in molecular docking study. To overcome this problem, some heterocyclic derivatives of chalcone have been designed. These heterocyclic derivatives show interactions similar to co-crystallized ligand, which means both terminal rings exhibit interactions with macromolecular receptor in molecular docking study. Moreover, some of the synthesized heterocyclic derivatives of chalcone show potent inhibitory activity when tested *in vitro* and compound **AD-4** ((*E*)-3-(3-nitrophenyl)-1-(pyridin-4-yl)prop-2-en-1-one) is observed as the most prominent inhibitory agent with 75.06% inhibition of PTP1B. Potent derivative **AD-4** also exhibits significant anti-hyperglycemic activity during *in vivo* evaluation in animal model.

Keywords: Anti-hyperglycemic, Chalcone, Heterocycles, PTP1B, Insulin, Diabetes

Diabetes mellitus is a very common metabolic disorder mainly associated with altered lipid metabolism, other complication such as myocardial infarction, hypertension, dyslipidemia and hyperglycemia also associated with diabetes mellitus[1]. The insulin resistance is one of the major issues observed in diabetes patients which occurs due to the inability of cells to propagate insulin signallaning[2-4]. Enzyme protein tyrosine phosphatase 1B (PTP1B) play major role in insulin signaling pathway, PTP1B modify insulin sensitivity and dephosphorylation of insulin receptor resulting initiation of pathogenesis of Type II diabetes. Literature study also revealed that inhibition of PTP1B reduces state of insulin resistant by modifying negative pressure on signaling pathway[5-7]. Therefore, it was suggested that medicinal agents having ability to inhibit negative regulation of PTP1B help to maintain plasma glucose level without inducing hypoglycemia[4-7]. The possible mode of action of PTP1B inhibitors as anti-diabetic agents is prolongation of half life of phosphorylated insulin receptor which ultimately enhances effects of insulin.

Chalcones or 1,3-diaryl-2-propen-1-ones are flavonoids, chemically composed by two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system. Chalcones are considered precursors of flavonoids and isoflavonoids in plants[8]. Chalcones and chalcone derivatives possesses diversified biological activities therefore researchers paid great attention towards this molecule for searching potent therapeutic agents against various diseases[9-11].

Heterocyclic derivatives of chalcone also contributed remarkably towards the development of novel synthetic agents since these nucleus offers different pharmacological activities such as; antimicrobial[12], antiamoebic[13], antidepressant[14] and anticancer[15] activities.

Considering these all facts in present work it was planned to design and synthesize some chalcones and their heterocyclic derivatives as PTP 1B inhibitors, further expected to elicit anti-hyperglycemic response.

Initially the 3D crystal structure (PDB ID: 1Q1M) of PTP 1B receptor retrieved from RCSB (Research Collaboratory for Structural Bioinformatics) data source. The co-crystallized ligand, "5-{2-fluoro-5-[3-(3-hydroxy-2-methoxycarbonyl-phenoxy)-propenyl]-phenyl}-isoxazole-3-carboxylic acid" bound with

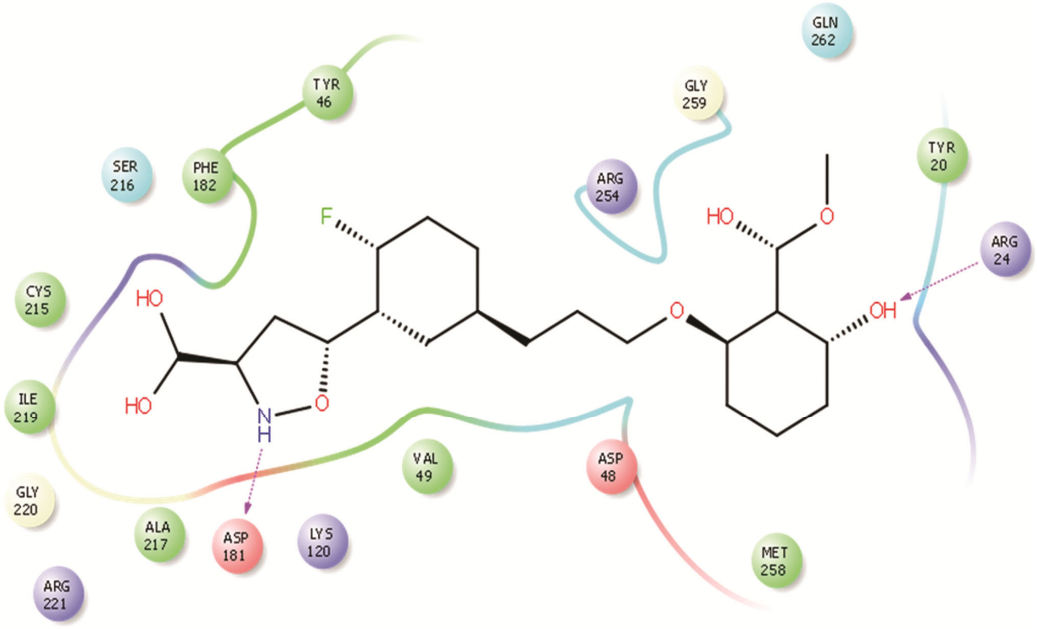
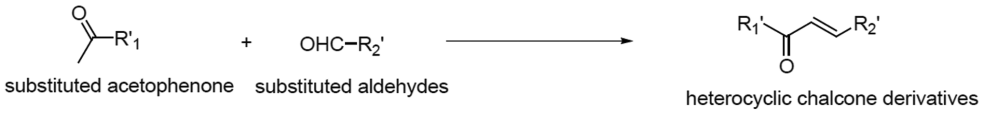
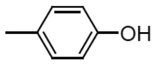
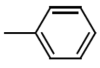
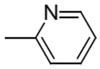
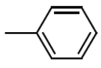
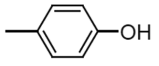
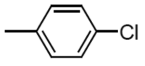
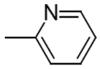
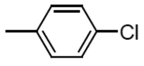
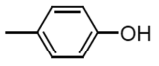
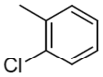
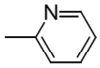
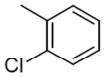
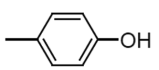
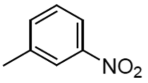
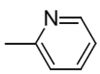
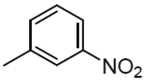
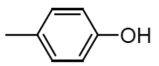
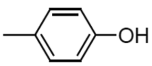
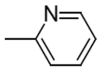
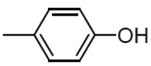


Fig. 1 — Interaction between ligand and PTP1B enzyme in the co-crystallized enzyme inhibitor complex (PDB ID: 1Q1M, 2.3 Å)



Compd	R_1'	R_2'	Compd	R_1'	R_2'
AJ-1			AD-1		
AJ-2			AD-2		
AJ-3			AD-3		
AJ-4			AD-4		
AJ-5			AD-5		

Scheme 1 — Synthetic route used for proposed derivatives

active site of enzyme (1Q1M) showed interaction with key amino acid residues as depicted in Fig. 1. Considering these interactions as prerequisite features of PTP 1B inhibitory agents, some chalcone and their heterocyclic derivatives were designed and tested for any possibility of interactions with binding sites of 1Q1M using molecular docking (Maestro) study. The ligands those exhibited desired interactions with receptor somewhat similar to co-crystallized ligand were further synthesized and evaluated for their PTP 1B inhibitory activities using *in vitro* model.

Experimental Section

Chemistry

The target derivatives were synthesized as mentioned in Scheme 1, using Claisen-Schmidt reaction between substituted benzaldehyde and acetophenone.

Synthesis of chalcones derivatives (AJ1-AJ5)

A solution of sodium hydroxide (30%) in water and rectified spirit was placed in a flask provided with a mechanical stirrer. The flask was immersed in a bath of crushed ice. Substituted acetophenone was poured

with constant stirring, substituted benzaldehydes were added to the solution. The temperature of mixture was kept at about 25°C and stirred vigorously until the mixture was thick enough to retard the stirring (approx. 6 hr). Reaction mixture was kept at 8°C overnight and product was filtered with suction using buchner funnel, washed with cold water until the washings were neutral to litmus. The crude product was recrystallized finally using ethanol.

Synthesis of heterocyclic derivatives of chalcones, AD1-AD5

Mixture of 4-acetylpyridine and substituted benzaldehydes in ethanol stirred using magnetic stirrer that after 40% solution of potassium hydroxide was added to the mixture, maintaining temperature of medium around 20 to 25°C. The reaction mixture was further stirred for 6 h; cooled and refrigerated overnight. Thereafter, it was poured into crushed ice and acidified with HCl. The precipitate of heterocyclic chalcones (AD1-AD5) was filtered, dried and recrystallized using rectified spirit.

Molecular docking studies

RCSB Protein Data Bank was used to retrieved Crystal structures of PTP1B (PDB codes: 1Q1M). Protein preparation was done using Discovery Studio 3.0 software package, hydrogen atoms were added and water molecules were removed from the structures. Schrödinger virtual tool was used to perform Glide docking experiment. Protein and ligand were used with rational geometry as 3D structures for Glide docking. Protein integrity was ensured and related corrections were made by deleting water molecules, hydrogen atoms were added followed by correct sequencing of bonds orders. The key amino acids such as; Asp, His and Lys were assigned as protonated and tautomeric (*p*H 7.4). The hydrogen atoms of crystal structures of PTP1B complexes were optimized using OPLS 2005 force field to minimize heavy atoms with in desired RMSD (0.3) [16].

***In vitro* PTP1B enzyme inhibitory activity**

Synthesized compounds were tested for their *in vitro* anti-hyperglycemic activity against PTP1B enzyme using colourimetric, PTP1B tyrosine Phosphatase drug discovery Assay kit obtained from Merck Millipore. Human recombinant PTP1B was used to perform PTP1B enzyme inhibitory activity, suramin provided in assay kit was used as controlled drug. Assay was performed as per the manufacturer's protocol using 96 well plates microtiter. Test compounds were dissolved in DMSO and free phosphate detected as per the principle of classic Malachite green assay[17]. The percentage inhibition of PTP1B enzyme by the test compounds was calculated by considering activity of the control tube (without inhibitor) as 100% using following formula:

% Activity = [Test Sample ($nmolPO_4^{2-}$) – time zero ($nmolPO_4^{2-}$)] × 100/
[Control ($nmolPO_4^{2-}$) – time zero ($nmolPO_4^{2-}$)]

***In vivo* anti-hyperglycemic activity evaluation in HFD/STZ induced T2DM model**

Streptozotocin induced anti-hyperglycemic activity was performed to ensure *in vivo* anti-diabetic potential of test compound AD-04 which was considered as valuable lead in earlier studies (molecular docking and *in-vitro* evaluation). Sprague-Dawley rats of either sex (body weight 200-250 g) were selected for study and Type 2 diabetes was induced as per standard protocol using streptozotocin (STZ) treated rat model of T2DM[18]. Streptozotocin (35 mg/kg) was administered intraperitoneally to the animals after the completion of two week of high-fat diet protocols. Fasting glucose estimation was performed to ensure induction of diabetes after two weeks. Animals were considered diabetic if they observed with glucose levels more than 140 mg/dl. Animals were divided into five groups (six in each) in a way so that their average basal plasma glucose levels remains approximately similar to each other. Test compound AD-04 was administered at a dose of 30 mg/kg while metformin was administered at a dose of 300 mg/kg through oral route. The normal control and diabetic control groups were treated with an equal amount of vehicle (0.5% Na-CMC). Serum glucose levels were measured after overnight fasting on day 0 (starting of treatment) and on 28th day of completion of treatment. The results expressed as mean ± SEM and data analysis was performed using two-way ANOVA followed by Bonferroni test. A value of $p < 0.05$ was considered statistically significant[19].

Results and Discussion

Chemistry

Mixture of 4-hydroxy acetophenone and substituted benzaldehydes was used to synthesize chalcone derivatives (AJ1-AJ5) while mixture of 4-acetylpyridine and substituted benzaldehydes was used to prepare heterocyclic derivatives of chalcone

(AD1-AD5). Spectral analysis was performed to establish structural features of synthesized compounds along with physicochemical characterization.

Melting points were determined using capillary melting point apparatus (Lab Hosp). The progress of reaction was monitored by TLC performed on silica Gel G coated plate. IR spectra were recorded in KBr on MB3000 (Make-ABB Bomen) spectrometer. The ^{1}H NMR spectra were recorded in DMSO-d_6 on Bruker Avance II 400 NMR spectrometer. The mass spectra were recorded on Jeol SX-102 mass spectrometer.

(E)-1-(4-Hydroxyphenyl)-3-phenylprop-2-en-1-one, AJ1: Yield 71%. ^{1}H NMR: δ 6.74 (1H, d, 15.7 Hz), 6.87 (2H, ddd, 8.3, 1.1, 0.4 Hz), 7.38-7.55 (6H, 7.44 (tt, 7.2, 1.3 Hz), 7.50 (d, 15.7 Hz), 7.45 (dddd, 7.9, 1.6, 1.3, 0.5 Hz), 7.43 (dddd, 7.9, 7.2, 2.0, 0.5 Hz)), 7.58 (2H, ddd, 8.3, 1.8, 0.4 Hz); MS: *m/z* 224.08.

(E)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one, AJ2: Yield 48%. ^{1}H NMR: δ 6.87 (2H, ddd, 8.3, 1.1, 0.4 Hz), 7.44-7.57 (5H, 7.49 (d, 15.7 Hz), 7.53 (ddd, 8.1, 1.4, 0.5 Hz), 7.54 (ddd, 8.1, 1.2, 0.5 Hz); MS: *m/z* 258.04.

(E)-3-(2-Chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one, AJ3: Yield 65%. ^{1}H NMR: δ 6.70 (1H, d, 15.7 Hz), 6.87 (2H, ddd, 8.3, 1.1, 0.4 Hz), 7.44-7.57 (5H, 7.49 (d, 15.7 Hz), 7.53 (ddd, 8.1, 1.4, 0.5 Hz); MS: *m/z* 258.04.

(E)-1-(4-Hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en- 1-one, AJ4: Yield 49%. ^{1}H NMR: δ 7.44-7.57 (5H, 7.49 (d, 15.7 Hz), 7.53 (ddd, 8.1, 1.4, 0.5 Hz), 7.54 (ddd, 8.1, 1.2, 0.5 Hz)), 7.58 (2H, ddd, 8.3, 1.8, 0.4 Hz); MS: *m/z* 269.07.

(E)-1,3-bis(4-Hydroxyphenyl)prop-2-en-1-one, AJ5: Yield 35%. ^{1}H NMR: δ 6.66 (1H, d, 15.6 Hz), 6.83-6.93 (4H, 6.86 (ddd, 8.3, 1.1, 0.4 Hz), 6.89 (ddd, 8.0, 1.7, 0.4 Hz)), 7.49-7.61 (3H, 7.53 (d, 15.6 Hz), 7.58 (ddd, 8.3, 1.8, 0.4 Hz)), 7.54 (2H, ddd, 8.0, 1.9, 0.4 Hz); MS: *m/z* 240.08.

(E)-3-Phenyl-1-(pyridin-4-yl)prop-2-en-1-one, AD-1: Yield 62%. ^{1}H NMR: δ 6.84 (1H, d, 15.6 Hz), 7.45-7.60 (5H, 7.52 (tt, 7.4, 1.5 Hz), 7.49 (dddd, 8.5, 1.6, 1.5, 0.4 Hz), 7.55 (dddd, 8.5, 7.4, 1.4, 0.4 Hz)), 7.75-7.84 (3H, 7.82 (ddd, 4.6, 1.6, 0.5 Hz), 7.80 (d, 15.6 Hz)), 8.74 (2H, ddd, 4.6, 1.9, 0.5 Hz); MS: *m/z* 209.08.

(E)-3-(4-Chlorophenyl)-1-(pyridin-4-yl)prop-2-en-1-one, AD2: Yield 63%. ^{1}H NMR: δ 7.52 (2H, ddd, 8.7, 1.3, 0.5 Hz), 7.74 (2H, ddd, 8.7, 1.8, 0.5 Hz), 7.74-7.83 (3H, 7.81 (ddd, 4.6, 1.6, 0.5 Hz); MS: *m/z* 243.05.

(E)-3-(2-Chlorophenyl)-1-(pyridin-4-yl)prop-2-en-1-one, AD3: Yield 58%. ^{1}H NMR: δ 7.39 (1H, ddd, 8.1, 7.6, 1.5 Hz), 7.47-7.57 (2H, 7.52 (ddd, 8.3, 1.5, 0.5 Hz), 7.52 (ddd, 8.3, 7.6, 1.4 Hz)), 7.74-7.83 (3H, 7.81 (ddd, 4.6, 1.6, 0.5 Hz), 7.78 (d, 15.6 Hz); MS: *m/z* 243.05.

(E)-3-(3-Nitrophenyl)-1-(pyridin-4-yl)prop-2-en-1-one, AD4: Yield 54%. ^{1}H NMR: δ 6.78 (1H, d, 15.6 Hz), 7.39 (1H, ddd, 8.1, 7.6, 1.5 Hz), 7.47-7.57 (2H, 7.52 (ddd, 8.3, 1.5, 0.5 Hz), 7.52 (ddd, 8.3, 7.6, 1.4 Hz)), 7.74-7.83 (3H, 7.81 (ddd, 4.6, 1.6, 0.5 Hz); MS: *m/z* 254.07.

(E)-3-(4-Hydroxyphenyl)-1-(pyridin-4-yl)prop-2-en-1-one, AD5: Yield 48%. ^{1}H NMR: δ 6.87 (ddd, 8.3, 1.1, 0.4 Hz)), 7.59 (2H, ddd, 8.3, 1.8, 0.4 Hz), 7.73-7.83 (3H, 7.81 (ddd, 4.6, 1.6, 0.5 Hz), 7.77 (d, 15.6 Hz); MS: *m/z* 225.08.

It was observed that position of the substituents affects rate of reaction greatly, formation of *para* substituted derivatives required lesser time than *ortho* and *meta* substituted chalcones. Compounds containing hydroxyl group on both ring at *para* position obtained with high yield and kinetic of reaction revealed that *ortho* and *para* directing effect of phenolic group offer faster completion of reaction[20,21]. Physicochemical characteristics of synthesized derivatives were mentioned in Table 1.

Structures of compounds were established using various spectral techniques such as; MS, NMR and IR. Elemental analysis also performed to calculate percentage of C; H and N. The NMR signal around δ 9.7

Table 1 — Physicochemical characteristics of synthesized derivatives

Compd	Mol. Formula	TLC (R_f*)	m.p. (°C)
AJ-1	$C_{15}H_{12}O_2$	R_f = 0.54	161-163
AJ-2	$C_{15}H_{11}ClO_2$	R_f = 0.53	190-192
AJ-3	$C_{15}H_{11}ClO_2$	R_f = 0.52	195-197
AJ-4	$C_{15}H_{11}NO_4$	R_f = 0.48	190-192
AJ-5	$C_{15}H_{12}O_3$	R_f = 0.58	202-205
AD-1	$C_{14}H_{11}NO$	R_f = 0.55	123-125
AD-2	$C_{14}H_{10}ClNO$	R_f = 0.59	145-147
AD-3	$C_{14}H_{10}ClNO$	R_f = 0.52	143-145
AD-4	$C_{14}H_{10}N_2O_3$	R_f = 0.58	148-150
AD-5	$C_{14}H_{11}NO_2$	R_f = 0.54	185-187

R_f* value in solvent system: chloroform:ethylacetate (2:3)

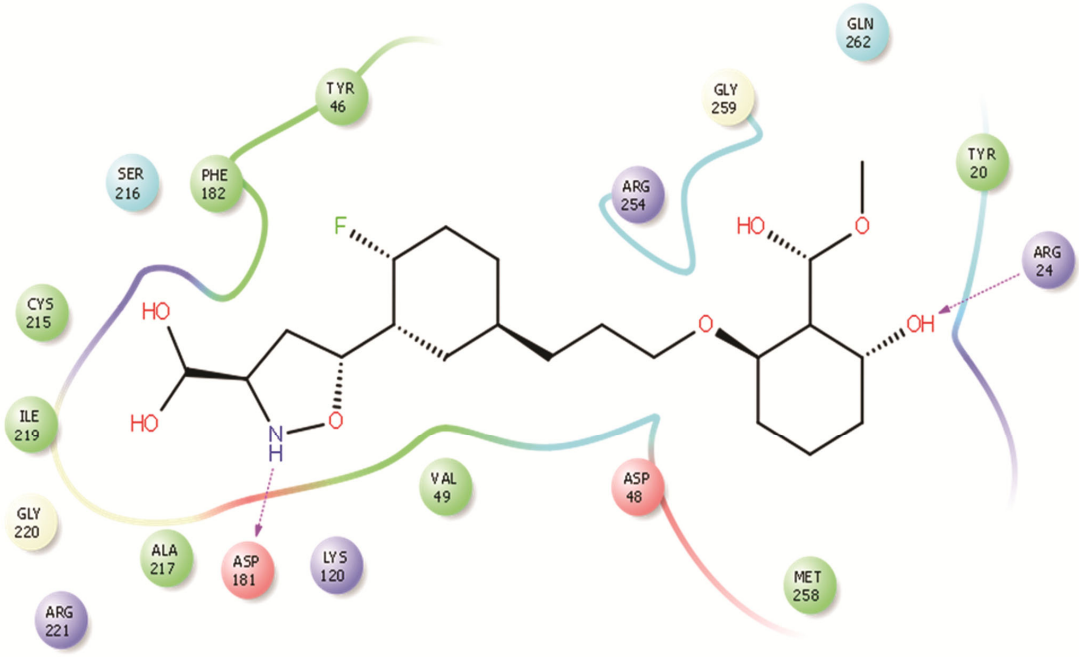


Fig. 2 — Binding mode of compound **AD-4** at PTP1B binding site (PDB ID: 1Q1M). Important amino acids are depicted as sticks, whereas the lead ligand is shown in green colour with nitrogen and oxygen atom in blue and pink, respectively. Brown dotted lines represent hydrogen bonding in the active site of PTP1B

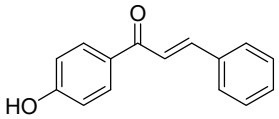
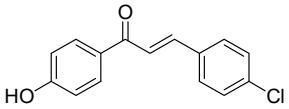
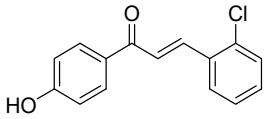
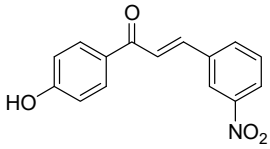
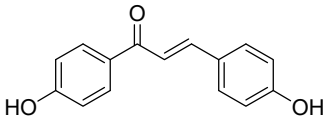
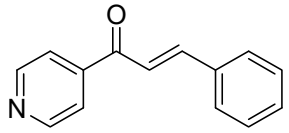
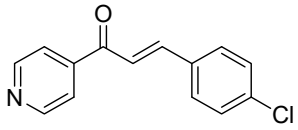
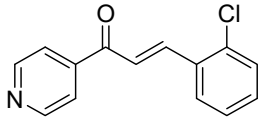
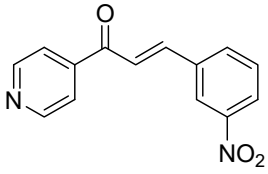
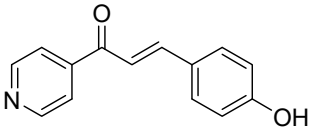
was assigned to OH proton of aryl ring. The signals for aromatic protons were observed around δ 6.62 - 7.71. IR spectra of all the compounds showed typical peaks of chalcone derivatives.

Molecular docking studies

Computer-aided docking method was used to forecast binding affinity of designed ligands in the binding region of crystal structures of PTP1B receptor thereby possible inhibitory activity. The co-crystallized ligands bound with active site of receptor and these bindings gives idea about the key interactions required for enzyme inhibitory activity. The designed ligands were expected to offers similar interactions with PTP1B receptor as like co-crystallized ligands. The crystal structure of PTP1B was prepared using protein preparation wizard of Schrödinger suite. Receptor grids were generated to fix active site using binding position of co-crystal ligand[22,23]. The standard precision followed by extra precision modes was set in Glide docking tool to acquire precise docking results. Glide docking was run to ascertain binding interactions of designed ligands with active sites of PTP1B (PDB ID: 1Q1M).

Literature study revealed five subpockets (A, B, C, D, and E) as PTP1B active site in the closed proximity. However A, B and C sites were found essential for insulin signaling functioning[24-26]. Interestingly chalcone compounds (AJ1-AJ5) showed interaction only in site A of enzyme; compounds AJ1, AJ2, AJ3 and AJ5 binds with Arg 221 while compounds AJ4 bind with ASP 181 through polar interaction. These chalcone compounds neither interact in Site B nor in Site C. However heterocyclic derivatives of chalcone exhibited residual interactions in both region; Site A as well as in Site C. Compounds AD1, AD2 and AD5 exhibited polar interaction with Arg 221 in Site A and hydrophobic interaction with Tyr 46 in Site C, fortunately compound AD4 depicted polar interactions in both region. Catalytic site A contained polar amino acids including Asp48 and Arg221, Fig. 2 depicted that compound **AD-4** ((*E*)-3-(3-nitrophenyl)-1-(pyridin-4-yl)prop-2-en-1-one) interacts with these catalytic residues. Oxygen of nitro group interacts with Asp48 while Nitrogen of pyridine ring of compound AD-4 interacts with Arg221. Moreover one aryl ring of compound AD-4 interact with surrounding Tyr46 residue of Site C, this interaction contributed for enhancing biological activity of proposed inhibitor. [16] The docking study revealed that most of the ligands bind with at least one catalytic site of PTP1B, however some heterocyclic derivatives of chalcone exhibited prominent interactions and compound AD-4

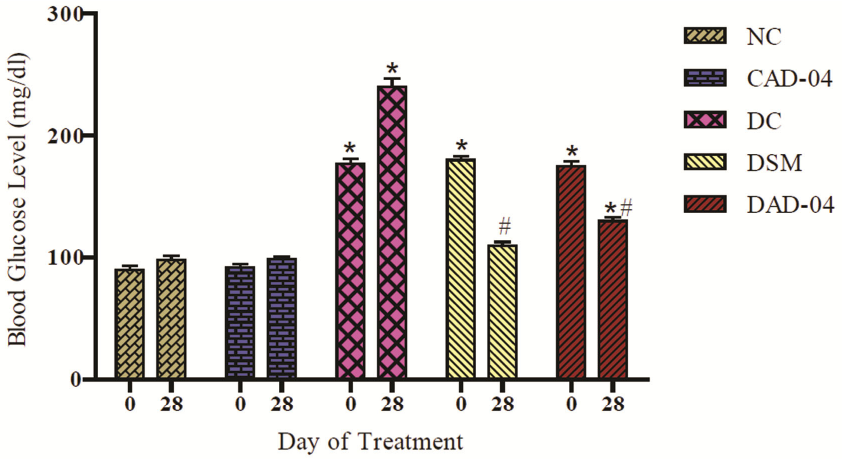
Table 2 — Results of *in vitro* PTP1B enzyme inhibitory activity

S. No.	Compd	Structure of target derivatives	% Inhibitory activity (30 μM)	IC_{50} value (μM)
1	**AJ-1**		42.05	–
2	**AJ-2**		43.25	–
3	**AJ-3**		40.16	–
4	**AJ-4**		49.86	–
5	**AJ-5**		45.14	–
6	**AD-1**		57.40	–
7	**AD-2**		44.57	–
8	**AD-3**		54.37	–
9	**AD-4**		75.06	9.72
10	**AD-5**		50.54	–
11	Suramin	–	23.04 (10 μM)	–

binds almost in similar manner (Fig. 2) as like co-crystallized ligand bound with crystal structure of PTP1B (Fig. 1). These interactions ensure probability of PTP1B inhibitory activity of proposed compounds.

In vitro PTP1B enzyme inhibitory activity

The inhibitory activity of synthesized compounds against protein tyrosine Phosphatase 1B was evaluated as per the manufacturer's protocol provided along with assay kit.[17] The synthesized compounds were tested at 30 μM concentration, most of the heterocyclic derivatives of chalcones (AD1, AD3, AD4 and AD5) exhibited ≥ 50% inhibition of PTP1B enzyme while chalcones derivatives (AJ1-AJ5) devoid off same potency as presented in Table 2. Compound **AD-4** ((*E*)-3-(3-nitrophenyl)-1-(pyridin-4-



*- significantly different from control ($p < 0.05$)
#- significantly different from diabetic control ($p < 0.05$)
CN – Normal Control animals, CAD-04 – Normal Control animals treated with AD-04 (30 mg/kg/p.o/day), DC - Diabetic Control animals, DSM - Diabetic animals treated with Standard metformin (300 mg/kg/p.o/day), DAD-04 - Diabetic animals treated with AD-04 (30 mg/kg/p.o/day)

Fig. 3 — Effects of compound **AD-04** at 30 mg/kg dose on the change of serum glucose levels in HFD/STZ rats after 28 days

yl)prop-2-en-1-one) was observed as most potent one with 75.06% inhibition of enzyme PTP1B. These findings suggests that compound AD4 can be developed as anti-hyperglycemic agent and to ensure this we further tested compound AD4 in animal model for its probable anti-hyperglycemic activity.

In vivo anti-hyperglycemic activity evaluation in HFD/STZ induced T2DM model

The *in vivo* anti-hyperglycaemic activity of compound AD-4 was estimated using streptozotocin induced type II diabetes model. [18] This study revealed significant reduction of elevated glucose levels in diabetic animals when treated with compound AD-4 (30 mg/kg) and standard drug metformin 300 mg/kg as shown in Fig. 3. There was no significant difference was observed in glucose level lowering capacity between the diabetic animals treated with compound AD-4 and animals treated with standard drug metformin, these finding suggests that compound AD-4 provides similar anti-hyperglycemic effect as like metformin.

Conclusion

In summary, chalcone and their heterocyclic derivatives were designed based on ligand (co-crystallized) and receptor complex information. Synthesized derivatives were evaluated for their *in-vitro* Protein Tyrosine Phosphatase 1B inhibitory potential followed by *in-vivo* anti-hyperglycemic efficacy. Compound (AD-4) was found as potent inhibitory agent against PTP1B (IC50 < 10 μM). The most active compound AD-4 exhibited desired binding interactions with catalytic site of PTP1B, as indicated by molecular docking studies. Moreover, compound AD-4 elicited appreciable *in vivo* anti-hyperglycemic efficacy in streptozotocin induced type II diabetes model. The finding of this study suggested that these heterocyclic derivatives of chalcone have excellent scope for further development as anti-hyperglycemic agents.

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Conflict of Interest

No conflict of interest is associated with this work.

References

1 Ahmad G, Mishra P, Gupta P, Yadav P, Tiwari P, Tamrakar A, Srivastava A & Mauryaa R, *Bioorg Med Chem*, 16 (2006) 2139.
2 Ala P J, Gonneville L & Hillman M C, *J Biol Chem*, 281 (2006) 32784.
3 Barsoum F F, Hosni H M & Girgis A S, *Bioorg Med Chem*, 14 (2006) 3929.
4 Block J H, Beale J M, *Organic Medicinal and Pharmaceutical Chemistry*, (Lippincott Williams & Wilkins) 2004, p. 1-2.
5 Boucher J, Kleinridders A & Kahn C R, *Perspect Biol*, 6 (2014) 009191.
6 Fioravanti R, Bolsaco A, Manna F, Rossi F, Orallo F, Ortuso F, Alcaro S & Cirilli R, *Eur J Med Chem*, 45 (2010) 6135.

7 Friesner R A, Murphy R B & Repasky M P, *J Med Chem*, 49 (2006) 6177.
8 Jin C, Liang Y, He H & Fu L, *Biomed Pharmacother*, 10 (2011) 1.
9 Jarag K J, Pinjari D V, Pandit A B & Shankarling G S, *Ultrason Sonochem,* 18 (2011) 617.
10 Khode S, Maddi V, Aragade P & Palkar M, *Eur J Med Chem*, 44 (2009) 1682.
11 Li R J, Wang J & Xu Z, *Chem Med Chem*, 9 (2014) 1012.
12 Martin B, Pallen C J, Wang J H & Graves D J, *J Biol Chem*, 260 (1985) 14932.
13 Montalibet J & Kennedy B, *Drug Disc Today Ther Strateg*, 2 (2005) 129.
14 Nowakowska Z, *Eur J Med Chem*, 42 (2007) 125.
15 Patil C B, Mahajan S K & Katti S A, *Int J Pharm Pharm Res*, 1 (2009) 11.
16 Rathish I G, Javed K, Ahmad S & Bano S, *Bioorg Med Chem Lett*, 19 (2009) 255.
17 Salmeen A, Andersen J N, Myers M P, Tonks N K & Barford D, *Mol Cell*, 6 (2000) 1401.
18 Scior T, García J, Melendez F, Abdallah H, Do Q & Bernard P, *Drug Des Devel Ther*, 4 (2010) 231.
19 Srinivasan K, Viswanad B, Asrat L, Kaul C L & Ramarao P, *Pharmacol Res*, 52 (2005) 313.
20 Tabbi A, Zafer A K, Dahmane T, Leyla Y, Zerrin C, Ozlem A, Merve B & Gulhan T Z, *Turk J Chem*, 40 (2016) 641.
21 Vintonyak V, Antonchick A, Rauh D & Waldmann H, *Curr Opin Chem Biol*, 13 (2009) 272.
22 Wrobel J, Li Z, Sredy J, Sawicki D, Seestaller L & Sullivan D, *Bioorg Med Chem*, 10 (2000) 1535.
23 Zhang M, Lv X-Y, Li J, Xu Z-G & Chen L, *Exp Diabetes Res*, 2008 (2008) 1. (https://doi.org/10.1155/2008/704045).
24 Zhang X, Jiang H, Li W, Wang J & Cheng M, *Comp Math Methods Med*, (2017) 1.
25 Zhao H, Liu G & Xin Z, *Bioorg Med Chem Lett*, 14 (2004) 5543.
26 Jia Z, Barford D, Flint A J & Tonks N K, *Science*, 268 (1995) 1754.