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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW HETEROCYCLIC DERIVATIVES OF CHALCONE AS ANTIHYPERGLYCEMIC AGENTS

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ABSTRACT: Protein tyrosine phosphatase 1B (PTP1B) is an important target for diabetes since inhibition of PTP1B offers therapeutic benefits in insulin-resistant diabetes. Considering this fact in present investigation various heterocyclic derivatives of chalcone were synthesized and evaluated for their PTP1B inhibitory activity as antihyperglycemic agents. Heterocyclic derivatives; isoxazoline (II A-II E), and pyrazoline (III A - III E / VIA-VIC) were synthesized through cyclization of chalcone intermediates and structures of final compounds were established using various spectral analysis techniques such as; IR, 1H-NMR and mass. Compounds were screened for their antihyperglycemic activity using sucrose loaded diabetic model. Isoxazoline derivatives offered potent antihyperglycemic response than correspondence pyrazoline derivatives. Compounds bearing isoxazoline ring II A and II E showed maximum % fall of blood glucose level than control group which was comparable to the standard drug metformin. The newer compounds VIA, VIB, and VIC also evaluated for their anti-hyperglycemic activities, compound VIC showed appreciable response (62.5% antihyperglycemic activity). The result of biological activity was also anticipated by molecular docking study which was performed to confirm PTP1B inhibitory potential of synthesized derivatives using molegro virtual docker (MVD) software.

INTRODUCTION: Diabetes mellitus is a very common metabolic disorder mainly associated with altered lipid metabolism, other complications 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 signalizing [2, 4].

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Enzyme protein tyrosine phosphatase 1B (PTP1B) play a major role in insulin signaling pathway, PTP1B modify insulin sensitivity and de-phosphorylation of insulin receptor resulting initiation of pathogenesis of Type II diabetes. A literature study also revealed that inhibition of PTP1B reduces state of insulin-resistant by modifying negative pressure on signaling pathways [5, 7].

Therefore it was suggested that medicinal agents having the 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 ant 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 of 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 possess 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 such as pyrazoline and isoxazoline also contributed remarkably towards the development of novel synthetic agents since this 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 synthesize novel heterocyclic derivatives of chalcones as PTP 1B inhibitors and antihyperglycemic agents.

MATERIALS AND METHODS: Melting points were determined using a 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 on avance II 400 (make-bruker) NMR spectrometer. The mass spectra were recorded on jeol SX-102 (make-waters) spectrometer.

Synthesis of Chalcones Derivatives (IA-IE): 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 the mixture was kept at about 25 °C and stirred vigorously until the mixture was thick enough to retard the stirring (approx. 6 h). The 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 Isoxazoline Derivatives (IIA-IIE): A mixture of substituted chalcones (IA-IE) and hydroxylamine hydrochloride in ethanol was taken in a round bottom flask. The reaction mixture was refluxed for 6 h on a water bath then kept overnight at 8 °C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain pure products (IIA-IIE).

4-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II A): Yield 63%, IR: 3232 (O-H str,), 3225 (C-H str. aliphatic), 1520 (C=N str. aromatic), 1483 (C=C str. aromatic), 810 (C-H def aromatic). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.83-7.53 (m, 6CH, aromatic ring), 5.0 (d, COH aromatic), 5.4 (m, 1H, CH), 2.87-3.73 (s, OCH_3). Mass spectra: m/z 269.04.

3-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II B): Yield 54%, IR: 3082 (O-H str.), 3225 (C-H str. aliphatic), 1520 (C=N str. aromatic), 1483 (C=C str. aromatic), 1319 (C-O-N str. aromatic). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.95-7.53 (m, 6CH, aromatic ring), 5.0 (d, COH aromatic), 5.3 (m, 1H, CH), 2.87-3.73 (s, OCH_3). Mass spectra: m/z 268.09.

2-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II C): Yield 60% (ethanol), IR: 3082 (O-H str.), 3225 (C-H str. aliphatic), 1520 (C=N str. aromatic), 1483 (C=C str. aromatic), 1319 (C-O-N str. aromatic). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.88-7.37 (m, 6CH, aromatic ring), 5.0 (d, COH aromatic), 5.3 (m, 1H, CH), 2.87- 3.73 (s, OCH_3). Mass spectra: m/z 268.

4- (3- (3,4-Dimethoxy phenyl) Isoxazol-5-Yl) Phenol (II D): Yield 61% (ethanol), IR: 2920 (O-H str.), 1682 (aromatic C=C str.), 1612 (aromatic C=N str.), 1058 (C-O-C str. asymmetric), 866 (C-H def. aromatic), 746 (C-H bend). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.88-7.31 (m, 6CH, aromatic ring), 5.0 (d, COH aromatic), 5.3 (m, 1H, CH), 2.18-3.73 (s, 2 OCH_3). Mass spectra: m/z 298.08

4-(3-(Benzo [D][1,3]Dioxol-5-Yl) Isoxazol-5 Yl) Phenol (II E): Yield 59% (ethanol), IR: 2920 (O-H str.), 1682 (aromatic C=C str.), 1612 (aromatic C=N str.), 1348 (C-O-N str. aromatic), 765 (C-H bend). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.7-7.31 (m, 6CH, aromatic ring), 5.0 (d, COH

aromatic), 5.3 (m, 1H, CH), 5.9 (d, CH_2). Mass spectra: m/z 283.11

Synthesis of Pyrazoline Derivatives (IIIA-IIIE): In a mixture of substituted chalcone (IA-IE) in ethanol, hydrazine hydrate was added dropwise in a round bottom flask. The reaction mixture was heated under reflux for 6 h on a water bath followed with addition of ice-cold water. The mixture was kept overnight at 8 °C.

The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain pyrazoline derivatives (III A-III E).

4-(3-(4-Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III A): Yield 60% (ethanol), IR: 3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3022 (C-H str. aliphatic), 1522 (C=C str.), 1420 (C=N str. aromatic), 820 (C-H bend, aromatic). ^{1}H-NMR: 7.5 (r, 4H, aromatic ring), 6.7-7.37 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87-3.7 (s, OCH_3), 13.7 (r, NH). Mass spectra: m/z 268.

3-(3-(4-Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III B): Yield 55% (ethanol), IR: 3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3025 (C-H str. aliphatic), 1690 (C=C str.), 1425 (C=N str. aromatic), 901 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.8-7.37 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87-3.7 (s, OCH_3), 13.7 (r, NH). Mass spectra: m/z 268.

2-(3-(4-Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III C): Yield 53% (ethanol), IR: 3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3025 (C-H str. aromatic), 1416 (C=N str. aromatic), 1352 (C=C str.), 910 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.79-7.37(m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87- 3.7(s, OCH_3), 13.7 (r, NH). Mass spectra: m/z 267.80.

4-(3-(3, 4-Dimethoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III D): Yield 58% (ethanol), IR: 3082 (O-H str.), 3232 (aromatic C-H str.), 1609 (N-H bend), 1520 (C=C str.), 1120 (C-O-C str. asymmetric), 910 (C-H bend), 876 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.79-7.31 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87-3.7 (s, $2OCH_3$), 13.7 (r, NH). Mass spectra: m/z 294.12.

4-(3-(Benzo [D][1, 3] Dioxol – 5 - Yl) -1H-Pyrazol -5-Yl) Phenol (III E): Yield 57% (ethanol), IR: 3082 (O-H str.), 3232 (aromatic C-H str.), 1609 (N-H bend), 1520 (C=C str.), 1495 (C-O-C str. asymmetric), 947(C-H bend), 875 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.79-7.31 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 5.9 (d, CH_2 in ring), 13.7 (r, NH). Mass spectra: m/z 282.11.

Synthesis of Novel Pyrazoline Derivatives (VI A VI C): Substituted chalcone (IA-IE) treated with Epichlorhydrine and Sodium hydride to yield intermediates IV A-IV C which on reacting with a substituted amine in methanol offers another intermediate compounds VA-VC. Finally, hydrazine hydrate was added dropwise in a mixture of VA-VC in ethanol. The reaction mixture was heated under reflux for 6 h on a water bath followed with addition of ice-cold water. The mixture was kept overnight at 8 °C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain newer pyrazoline derivatives (VI A-VI C).

1-(Tert - Butylamino) – 3 - (4 - (3 - (4 - Methoxy phenyl)-4, 5-Dihydro-1H-Pyrazol-5-Yl) Phenyl) Propan-2-Ol (VI A): Yield 58% (ethanol), IR: 3247 (O-H str.), 3228 (C-H str.), 3022 (C-H str. aliphatic), 1522 (C=C str.), 1420 (C=N str. aromatic), 823 (C-H bend, aromatic). ^{1}H NMR: δ 1.69 (2H, dtt, J = 13.2, 6.9, 1.7 Hz), 2.29 (4H, ddt, J = 9.9, 6.7, 1.7 Hz), 5.79 (2H, ddd, J = 6.2, 1.8, 1.7 Hz). Mass spectra: m/z 381.

1-(Buty lamino)-3-(4-(3-(4-Methoxy phenyl)-4,5 Dihydro-1H-Pyrazol-5-Yl) Phenyl) Propan-2-Ol (VI B): Yield 53% (ethanol), IR: 3244 (O-H str.), 3227 (C-H str.), 3023 (C-H str. aliphatic), 1520 (C=C str.), 1423 (C=N str.), 824 (C-H bend, aromatic). ^{1}H NMR: δ 0.85-0.90 (6H, 0.88 (d, J = 6.7 Hz), 0.88 (d, J = 6.7 Hz)), 1.74 (1H, septt, J = 6.7, 5.5 Hz), 2.57-2.61 (2H, 2.59 (d, J = 5.5 Hz), 2.59 (d, J = 5.5 Hz)), 2.84-2.88 (2H, 2.86 (d, J = 5.9 Hz), 2.86 (d, J = 5.9 Hz)), 2.88-2.97 (3H, 2.92 (dd, J = 8.1, 6.3 Hz), 2.95 (d, J = 7.2 Hz), 2.95 (d, J = 7.2 Hz)), 3.04 (1H, dd, J = 6.3, 4.3 Hz), 3.80 (3H, s), 3.96 (1H, tt, J = 7.2, 5.9 Hz). Mass spectra: m/z 382.

1-(Tert-Butylamino)-3-(3-(3-(4-Methoxy phenyl) -4,5-Dihydro-1H-Pyrazol-5-Yl) Phenyl)Propan-2-Ol (VI C): Yield 59% (ethanol), IR: 3244 (O-H str.), 3227 (C-H str.), 3023 (C-H str.), 1520 (C=C str.), 1423 (C=N str.), 824 (C-H bend). ^{1}H NMR: 2.95 (d, J = 7.2 Hz), 2.95 (d, J = 7.2 Hz), 3.04 (1H, dd, J = 6.3, 4.3 Hz), 3.80 (3H, s), 3.96 (1H, tt, J = 7.2, 5.9 Hz), 7.12-7.24 (4H, 7.21 (ddd, J = 8.2, 1.4, 0.6 Hz), 7.15 (ddd, J = 8.2, 1.3, 0.6 Hz)). Mass spectra: m/z 381.

Anti-Hyperglycemic Activity (Effect on Sucrose Loaded Diabetic Model): Compounds were tested for the effect on % fall of blood glucose level in mice of average body weight 40-50 gm. The blood glucose levels of all animals were checked after overnight fasting (16 h) by the biochemical analyzer (ANOVA 2021). Animals showing blood glucose levels between 60-80 mg/dl were divided into groups of three animals in each.

Animals of experimental groups were administered the suspension of the synthetic compounds orally (made in 0.1% CMC) at a dose of 100 mg/kg. Animals of control were given an equal amount of 0.1% CMC.

A sucrose load was given to each animal orally exactly after 30 min post administration of the test sample. The blood glucose level of each animal was checked. Animals of standard group were given metformin and % anti-hyperglycemic activity was calculated by comparing blood glucose level of experimental and control group.

Molecular Docking Study: Molegro virtual docker was used for molecular docking study, PDB ID: 1Q1M served as 3D crystal structure for PTP1B receptor. Deletion of unwanted atoms, removal of water molecules and side-chain optimization was performed. The grid was generated around the binding site of co-crystallized ligand and docking calculation was done using default parameters and best conformational poses were generated for each compound.

RESULTS AND DISCUSSION:

Chemistry: The target derivatives were synthesized as mentioned in scheme 1; the first step involved the synthesis of chalcones by claisen-schmidt reaction. The diaryl isoxazoline and pyrazoline derivatives were synthesized in next step *via* cyclization of chalcones intermediates.

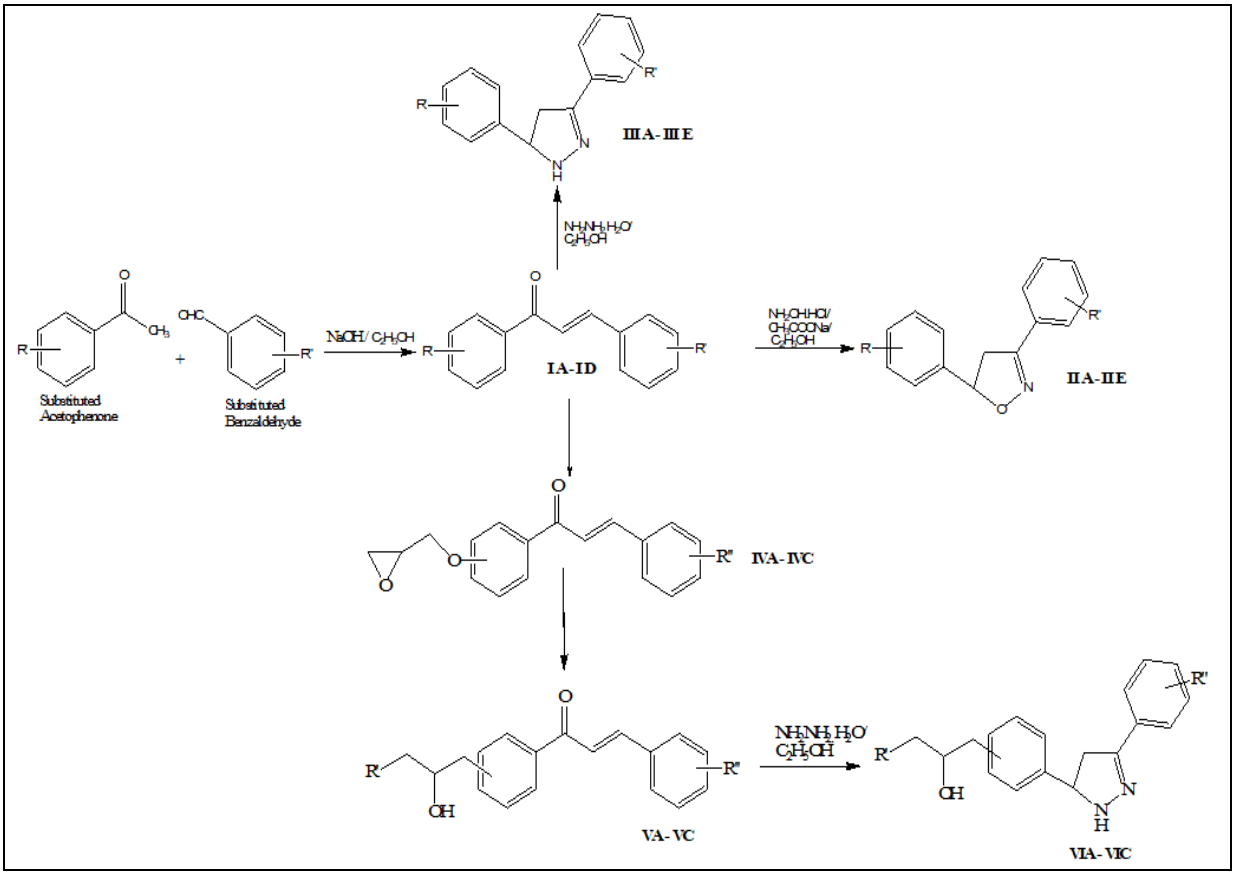

FIG. 1: SYNTHETIC ROUTE OF PROPOSED ISOXAZOLINE AND PYRAZOLINE DERIVATIVES

It was observed that the 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 kinetics of reaction revealed that ortho and para directing effect of phenolic group offer faster completion of reaction for compound II A, II D, III A and III D. Nucleophilic attack on carbon-carbon double bond at β position greatly affected by formation of aryl hydrazone during refluxing process. The different substituents on aryl ring affect rate of reaction due to their varying electron-withdrawing capacity which modulate electropositive character of β carbon; thus increases in positive character of β carbon by electron-withdrawing substituents on aryl ring for compounds II A, II D, III A, and III D resulted faster completion of reaction [16, 17]. The physicochemical characteristics of synthesized derivatives were mentioned in **Table 1.**

TABLE 1: PHYSICOCHEMICAL CHARACTERISTICS OF SYNTHESIZED DERIVATIVES

S. no.	Compound code	R'	R''	Mol. formula	Melting point(°C)	R_f * value
1	II A	4' - OH	4- OMe	$C_{16}H_{13}NO_3$	90-95 °C	0.79
2	II B	3' - OH	4- OMe	$C_{16}H_{13}NO_3$	95-100 °C	0.66
3	II C	2' - OH	4- OMe	$C_{16}H_{13}NO_3$	96-101 °C	0.68
4	II D	4' - OH	3,4 - OMe	$C_{17}H_{15}NO_4$	100-105 °C	0.71
5	II E	4' - OH	3,4 - Methylenedioxy	$C_{16}H_{11}NO_4$	167-168 °C	0.63
6	III A	4' - OH	4- OMe	$C_{16}H_{14}N2O_2$	170-175 °C	0.73
7	III B	3' - OH	4- OMe	$C_{16}H_{14}N2O_2$	160-165 °C	0.47
8	III C	2' - OH	4- OMe	$C_{16}H_{14}N2O_2$	161-166 °C	0.66
9	III D	4' - OH	3,4 - OMe	$C_{17}H_{16}N2O_3$	180-185 °C	0.88
10	III E	4' - OH	3,4 - Methylenedioxy	$C_{16}H_{12}N2O_3$	163-164 °C	0.67
11	VIA	4'-$NHC(CH_3)_3$	4- OMe	$C_{23}H_{31}N3O_2$	153-154 °C	0.68
12	VIB	4'-$NH(CH_2)_3CH_3$	4- OMe	$C_{23}H_{31}N_3O_2$	165-156 °C	0.65
13	VIC	3'-$NHC(CH_3)_3$	4- OMe	$C_{23}H_{31}N_3O_2$	143-144 °C	0.75

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

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

The single proton of pyrazoline-CH appeared at δ value 3.07 ppm. Spectral data of each compound presented individually in experimental section. The NMR signal around δ value 9.7 ppm was assigned to OH proton of aryl ring. The signals for aromatic protons were observed around 6.62 - 7.71 ppm.

IR spectra of all the compounds showed (C-N) stretch at 1577-1591 cm^{-1} for pyrazoline moiety. The NH band observed at 3291–3079 cm^{-1}, signals for C=C bands were observed at 1587–1303 cm^{-1}.

Anti-Hyperglycemic Activity (Effect on Sucrose Loaded Diabetic Model): All the compounds were evaluated for their *in-vivo* ant hyperglycemic activity using sucrose loaded diabetic model and fall in blood glucose level was measured as ant hyperglycemic activity of synthesized derivatives. Most of the synthesized derivatives revealed appreciable antihyperglycemic activity however isoxazoline derivatives showed more potent efficacy than pyrazoline derivatives **Table 2**.

TABLE 2: RESULT OF *IN-VIVO* ANTI-HYPERGLYCEMIC ACTIVITY OF SYNTHESIZED DERIVATIVES

S. no.	Compounds	% Antihyperglycemic activity
1	II A	71.0
2	II B	51.5
3	II C	52.0
4	II D	68.0
5	II E *	73.1
6	III A	62.5
7	III B	49.5
8	III C	53.0
9	III D	48.8
10	III E	65.4
11	VIA	56.5
12	VIB	47.0
13	VIC	62.5
14	Metformin (standard)	69.3
15	Gum acacia (control)	-----

Data presented as % ant hyperglycemic effect on comparison with control group * indicates a most potent compound

Compound IIA and IIE possessed potent response with 71 and 73.1% anti-hyperglycemic effect respectively.

The novel compounds VIA, VIB and VIC were also investigated for their antihyperglycemic activities, compound VIC showed prompt ant hyperglycemic activity than compounds VIA and VIB. The antihyperglycemic effect of synthesized derivatives may be due to the presence of central heterocyclic ring which offers most favorable binding poses with enzyme PTP1B [18]. Hydroxy substitution present in compound IIA contributed towards polar interaction with binding sites of enzyme thus offered prompt activity.

Similarly compound having bulky methoxy group offers confined rigid proximity to enhance drug-receptor interactions therefore compound IIE also showed remarkable anti-hyperglycemic effect comparable to the standard drug metformin [19].

Molecular Docking Studies: The findings of *in-vitro* and *in-vivo* studies further, rationalized by molecular docking study using molegro virtual docker software and 3D crystal structure of PTP1B receptor (PDB ID: 1Q1M) was obtained from RCSB protein data bank (PDB) [20, 21].

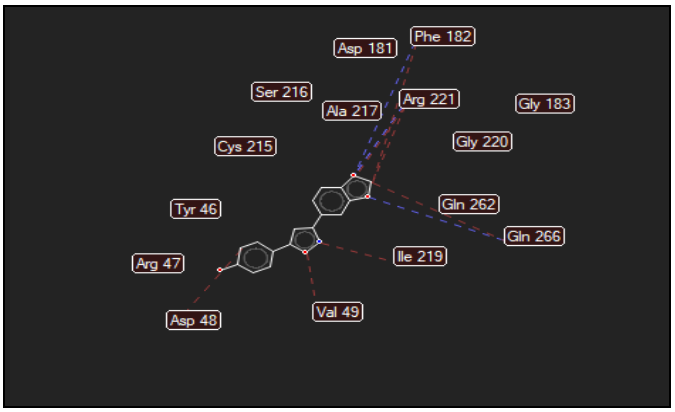

FIG. 2: INTERACTION OF COMPOUND IIE WITH BINDING SITES OF RECEPTOR PTP1B RECEPTOR (PDB ID: 1Q1M)

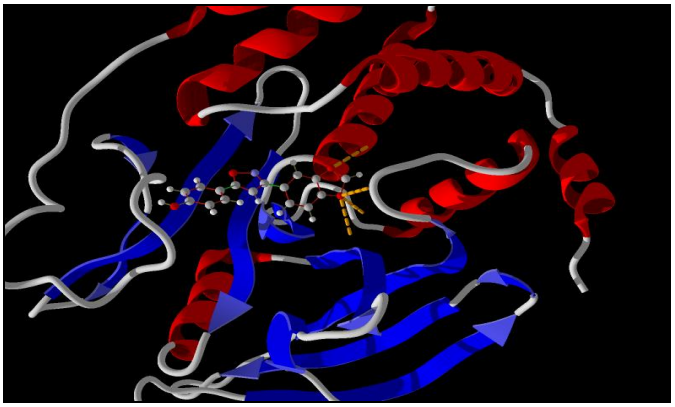

FIG. 3: DOCKING POSE OF COMPOUND IIE WITH RECEPTOR PTP1B RECEPTOR (PDB ID: 1Q1M)

The molecular docking study revealed the interaction between compound II E and active sites of receptor as shown in **Fig. 2** and **3**. This binding affinity may be due to the formation of hydrogen bond between amino acid residue of receptor and hydrophilic group of potent compound II E.

CONCLUSION: While considering the synthesized compounds of this series we may conclude that compound II E was found to be the most potent compound for anti-hyperglycemic activity. The results of present study have suggested that the isoxazoline and pyrazoline derivatives of chalcone have excellent scope for further, development as commercial antihyperglycemic agents.

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CONFLICTS OF INTEREST: No conflicts of interest associated with this work.

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