

# Synthesis of Cyclopyrrolidine Clubbed with Oxadiazole Bases and Evaluation of their Anti-Diabetic Activity through *in vivo* Model

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## ABSTRACT

**Background and Aim:** Based on inhibitors of DPP-IV, there is a fantastic method for creating anti-diabetic medications. These inhibitors regulate diabetic patients' blood sugar levels to prevent difficulties with their health. In the current work, we created a brand-new series of compounds Cyclopyrrolidine clubbed with oxadiazole bases. **Materials and Methods:** Cyclopyrrolidine clubbed with oxadiazole bases (B-1 to B-16) were synthesized and characterized through IR, NMR, mass spectrometry, and elemental analysis. Docking studies were performed to assess interactions and binding modes of synthesized hits at the binding site of receptor DPP-4 (PDB 3W2T). Using vildagliptin as a standard drug, six of the synthesized compounds were tested for their antidiabetic activity in diabetic rats induced with HFD-STZ-Nicotinamide. **Results:** The results showed that compound B-XIV (220\*4.56B) resulted in the greatest reduction in blood glucose level from all synthesized compounds compared to that of vildagliptin (215\*7.52B) in HFD-STZ-Nicotinamide. Other compounds showed moderate to good antihyperglycemic activity. **Conclusion:** From the presents work it can be concluded that synthesized compounds possess good DPP-IV inhibitory activity. Compounds containing electron-withdrawing groups (chlorine, nitro, methoxy) were displayed a good anti-diabetic effect than electron-donating groups (methyl, hydroxyl). Oxadiazole derivatives could be used for further development to obtain more promising drug candidates.

**Keywords:** Furadiazole, Hyperglycaemic, HFD-STZ-Nicotinamide.

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**Received:** 02-10-2022;

**Revised:** 30-03-2023;

**Accepted:** 08-06-2023.

## INTRODUCTION

Since the early 1970s, 1,2,4-oxadiazole heterocycles have been extensively investigated, yielding a variety of bioactive compounds, including anti-cancers,<sup>1</sup> anti-inflammatory,<sup>2</sup> anticonvulsant,<sup>3</sup> antiviral,<sup>4</sup> antibacterial,<sup>5</sup> antifungal,<sup>6</sup> anti-depressant,<sup>7</sup> anti-angiogenic,<sup>8</sup> analgesic,<sup>9</sup> anti-insomnia, anti-oedema,<sup>10</sup> anti-parasitic,<sup>11</sup> anti-Alzheimer<sup>12</sup> and anti-diabetic.<sup>13</sup> In addition, they showed inhibition of dipeptidyl peptidase IV,<sup>14</sup>  $\alpha$ -Glucosidase,<sup>15</sup>  $\alpha$ -Amylase,<sup>16</sup> Protein tyrosine phosphatase 1B.<sup>17</sup> A number of 1,2,4-oxadiazoles were screened as GLP19 (Glucagon-Like Peptide 1),<sup>18</sup> PPAR (peroxisome proliferator-activated receptor) alpha/gamma agonists,<sup>19</sup> GPR40 (G-Protein Receptor 40)<sup>20</sup> agonists as a antidiabetic activity.

Recently, GLP-1 has been identified as a potential target for treatment of T2DM. Gut hormone GLP-1 increases insulin

secretion after eating. GLP-1 has been shown to improve glycemic control in patients with Type 2 diabetes.<sup>21</sup> As GLP-1 cleaves its N-terminal, DPP-IV controls its activity [7-36]-amide to form GLP-1[9-36]-amide, an inert compound. This method can be used to increase GLP-1 in the blood by inhibiting DPP-IV.<sup>22</sup> As a result, the investigation of DPP-IV inhibitors as possible treatments has been devoted a significant amount of time and effort as shown in Figure 1.

## MATERIALS AND METHODS

ChemSketch software was used to simulate the 2D structures of the compounds, and AutoDock version 1.5.6 was used to dock the hits. A protein (PDB NO: 3W2T) was used as DPP-IV. Chemicals of analytical grade came from Nice Chemicals Pvt. Ltd., (India), Fizermerck (India), M Lychem chemical (India), and Poona chemical (India). We used the chemicals and solvents in their original forms, without purification.

Using Thin-Layer Chromatography (TLC), a reaction was monitored to determine if the reactants had been consumed and if a new product had been formed. Using the Labronics LT-115 digital melting point apparatus, we measured the melting



DOI: 10.5530/ijper.57.3s.85

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points of open capillary tubes. A silica gel cartridge (230-400 mesh, 40 m silica) was used to purify compounds using column chromatography. A Bruker FTIR was used to capture these FTIR spectra. Analyses of the synthesized compounds were conducted using  $\text{CDCl}_3$  (unless specified), TMS as an internal reference (chemical deviation, ppm) and SND 400 MHz instruments (chemical deviation, ppm) 100183-SND and 100186-SND, respectively). It was conducted by Thermo Finnigan. Only 4% of theoretical values were obtained in the elemental analysis.

### Synthesis of procedure for B-I to BXVI derivatives

a-chloro sulphonic chloride, sodium carbonate (3.0 mmol) in dichloromethane:water, stirred for 16 hr at room temperature.

b-1-ethyl-3-(3 dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.5 mmol) and 1-hydroxy benzotriazole (HOBT) (1.0 mmol) in dichloromethane added to the sample at 10 to 15°C (duration 5.0).

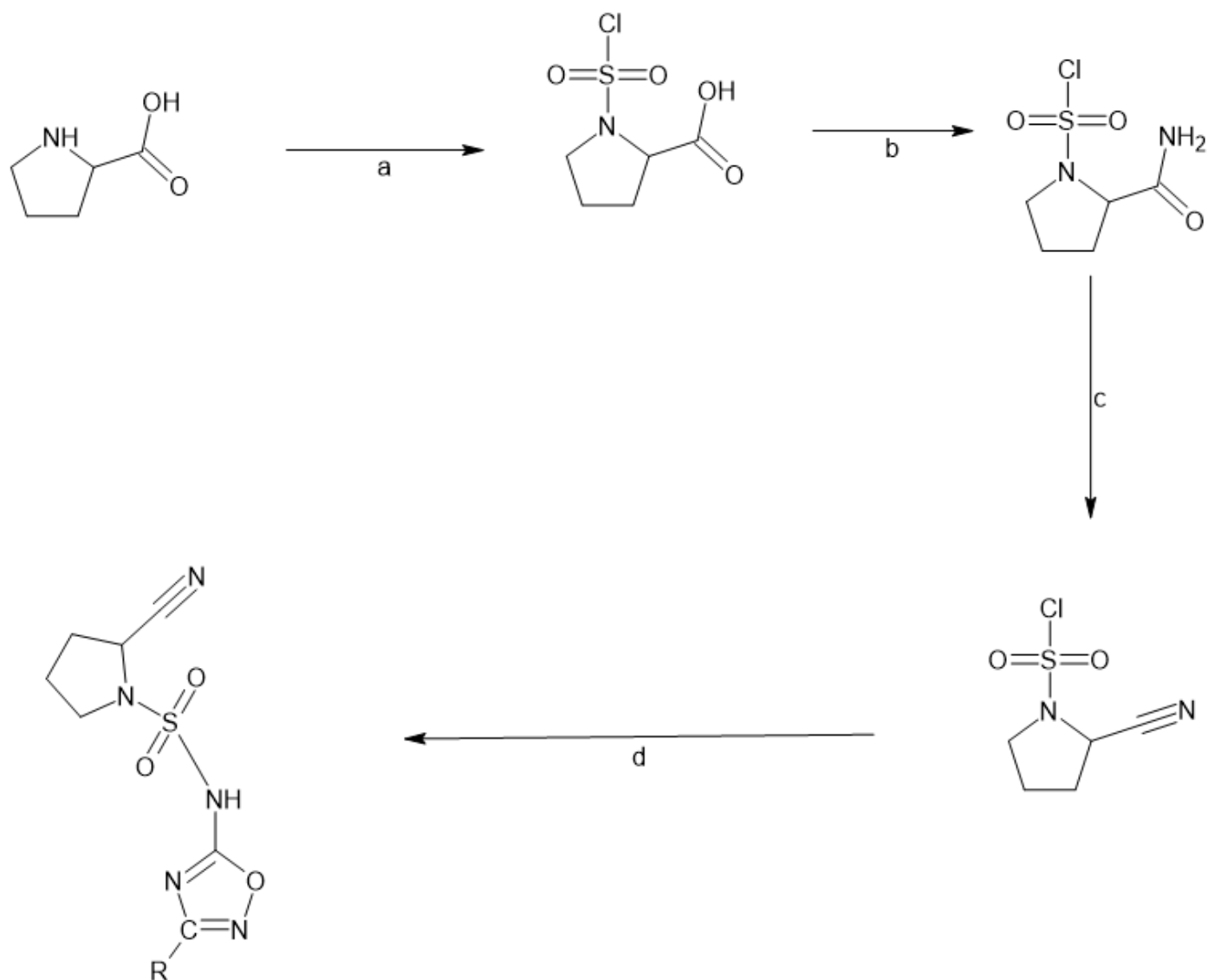
c-A mix of trifluoroacetic anhydride (2 mmol) and tetrahydrofuran (10 mL) was stirred at room temperature for 5 hr.

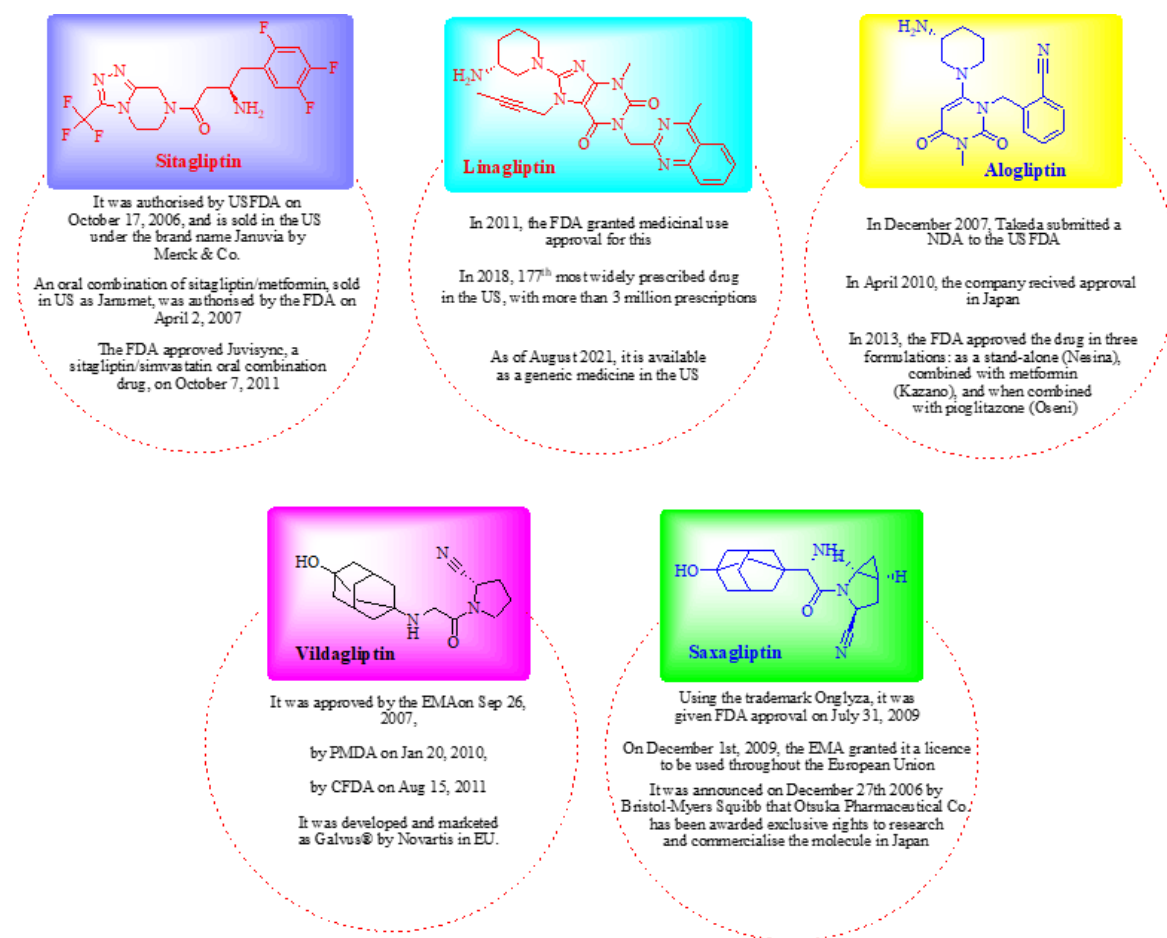
d-oxadiazole derivative compound (1.5 mmol) was refluxed with anhydrous potassium carbonate for 2 hr.

R=4-Hydroxy Phenyl, 3-Chloro Phenyl, 4-Nitro Phenyl, 2-Chloro Phenyl, 2-Acetoxy Phenyl, 4-Bromo Phenyl, 4-Chloro Phenyl, 2-Bromo Phenyl, 4-Methyl Phenyl, 3-Methyl Phenyl, 2-Nitro Phenyl, 4-Amino Phenyl, Trifluoromethyl Phenyl, 3,4-Dimethoxy Phenyl, 2-Hydroxy Phenyl, 4-Methoxy Phenyl.

### Synthesis 1-(chlorosulfonyl) pyrrolidine-2-carboxylic acid

As monitored by TLC, water was added to L-proline (1.0 mmol) and sodium carbonate (3.0 mmol) in a dichloromethane (1:1) solution and the mixture was stirred at room temperature for 16 hr until the reaction was completed. After the reaction was complete, the reaction mixture was washed with petroleum ether





**Figure 1:** The structures of clinically approved DPP-IV inhibitors.

(20 mL), then acidified with concentrated hydrochloride to a pH of acid. After filtering, the white solid was washed several times with water, dried, and observed on a single point of silica gel.<sup>23,24</sup>

Yield: 52%; Melting point: 118 - 120°C; IR (KBr): 1200(S=O sym), 1400(S=O asym), 600(C-Cl), 1200(S=O sym), 1400(S=O asym), 1450 (CH<sub>2</sub>), 1600 (C-H), 3550 (COOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.2-2.4(m,6H), 3.6 (s,1H), 11.4 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 22.3, 28.3, 62.3, 70.3, 174; ESI MS (*m/z*): 214.09[M+H]; Anal. Calcd. For found C<sub>5</sub>H<sub>8</sub>ClNO<sub>4</sub>S: C (28.11%), H (3.77%), N (6.56%).

### Synthesis 2-carbamoyl pyrrolidine-1-sulfonyl chloride

As a result, the mixture of dicyclohexylcarbodiimide in methylene chloride was connected to the mixture of phase-i a) in dichloromethane (10 mL solution) in a (1mmole) gradually at 10-15°C (duration 5.0 min), and the solution was stirred at room temperature for 5 hr. Stir gently for 1 hr with 5.0 mm of bicarbonate. Thin-layer chromatography analysis of 5% methanol, 3 percent chloroform, 3% anisaldehyde, and 2% iodine. After the process was completed, the sample was stirred in, and the residues were cleaned with dichloromethane. After collecting and pooling the filtrates, they were washed twice with water,

dried over anhydrous sodium sulphate, and evaporated under decreased pressure to provide a crude product that was then purified using silica gel by column chromatography. With ethyl acetate used as eluent, silica gel has been spotted with a single spot when tested with the pure required product.<sup>23</sup>

Yield: 58%; Melting point: 140-147°C; IR (KBr): 600 (C-Cl), 1200(S=O sym), 1400(S=O asym), 1450(CH<sub>2</sub>), 1600(C-H), 1650 (NH<sub>2</sub>-C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.64-2.8 (m,6H), 3.7 (s,1H), 7.21(s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 21.9, 28.3, 62.3, 71, 176.7; ESI MS (*m/z*): 214 [M+2H]; Anal. Calcd. For found C<sub>5</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>3</sub>S: C (28.22%), H (4.22%), N (13.12%).

### Synthesis 2-cyanopyrrolidine-1-sulfonyl chloride

Trifluoroacetic anhydride (2.0 mmol) suspension in tetrahydrofuran (10 mL) was added to amide (1.0 mmol) at 0-5°C and was mixed for 4 hr at room temperature. The response was tracked using thin-layer chromatography. Ammonium bicarbonate (7 mmol) was added (after completion of reaction) to the solution (later 15 min). The mixture was condensed in vacuum at 40°C and stirred for 1 hr at room temperature, then purified using dichloromethane and methanol (95:5) as elution to give 2-cyano-pyrrolidine-1-sulfonyl chloride as a white solid pure desired product and identified at a single point on silica

gel using dichloromethane: methanol (95:5) as elution to give 2-cyano-pyrrolidine-1-sulfonyl chloride as a white solid pure desired product.<sup>24</sup>

Yield: 55%; Melting point: 65-67°C; IR (KBr): 650 (C-Cl), 1200 (S=O sym), 1400 (S=O asym), 1450 (CH<sub>2</sub>), 1600 (C-H), 2200 (-16); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.64-2.8 (m,6H), 3.8 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 30.2, 52.8, 62.2, 116.2; ESI MS (*m/z*): 195 [M+H]; Anal. Calcd. For found C<sub>5</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub>S: C (30.80%), H (3.60%), N (14.32%).

### Catalyst-free Synthesis of 2-cyano-N-(5-substituted-oxadiazol-3-yl)pyrrolidine-1-sulphonamide

3-amino-5-substituted-1,2,4-oxadiazole (2 mmol) (Step-I amine compound) and 2-cyanopyrrolidine-1-sulfonyl chloride (1 mmol) were added to ethanol (2 mL) at room temperature and stirring was continued until the reaction was complete (monitored by TLC). It was filtered and the residue was washed with ethyl acetate. We collected the filtrate and evaporated the solvent under reduced pressure to give the crude product. Using ethyl acetate and petroleum ether as stationary phases, our crude product was purified by column chromatography (7:3) as a mobile phase to yield the product.<sup>24,25</sup>

R=4-Hydroxy Phenyl, 3-Chloro Phenyl, 4-Nitro Phenyl, 2-Chloro Phenyl, 2-Acetoxy Phenyl, 4-Bromo Phenyl, 4-Chloro Phenyl, 2-Bromo Phenyl, 4-Methyl Phenyl, 3-Methyl Phenyl, 2-Nitro Phenyl, 4-Amino Phenyl, 4-Trifluoromethyl Phenyl, 3,4-Dimethoxy Phenyl, 2-Hydroxy Phenyl, 4-Methoxy Phenyl.

## RESULTS

### 2-cyano-N-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 82%; Melting point: 156-158°C; IR (KBr): 1100(C=O), 1250(C-O), 1350 (O-H), 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H.), 2250(-145), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.80 (m,6H), 3.8 (s,1H), 6.88 (d,2H), 7.90 (d,2H), 9.67 (s,1H), 10.5 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 20-30, 50, 55, 56.1, 125-135, 144.6, 164.5-169.3; ESI MS (*m/z*): 388.06[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>S: C (46.56%), H (3.91%), N (20.88%).

### N-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-cyano pyrrolidine-1-sulfonamide

Yield: 84%; Melting point: 120-122°C; IR (KBr): 780(C-Cl), 1100(-C=O), 1450(CH<sub>2</sub>), 1550(-S=O), 1650(-C-H), 2250(-, 1), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40- 2.8 (m,6H), 3.8 (s,1H), 8.16(m,1H), 7.97(d,2H), 7.48(s,1H), 10.5 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 20.9, 29.3, 45.6, 45-55, 55, 116.2, 134, 125-135, 164.5-169.3; ESI MS (*m/z*): 354.78[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub>S: C (44.13%), H (3.42%), N (19.8%).

### 2-cyano-N-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 85%; Melting point: 168-170°C; IR (KBr): 1100(C=O), 1400(-NO<sub>2</sub>), 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-C≡N), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.8(m,6H), 3.8(s,1H), 8.3(d,2H), 8.87(d, 2H), 10.58(s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 20.9, 29.3, 45.6, 45-55, 55, 116.2, 134, 125-135, 164.5-169.3; ESI MS (*m/z*): 366.05[M+2H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>N<sub>6</sub>O<sub>5</sub>S: C (42.86%), H (3.32%), N (23.07%).

### N-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-cyano pyrrolidine-1-sulfonamide

Yield: 80%; Melting point: 125-127°C; IR (KBr): 680(C-Cl), 1050(C=O), 1455(CH<sub>2</sub>), 1560(C-H), 1600(S=O), 2200(-C≡N), 3050(CH), 3300(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.80 (m,6H), 3.8 (s,1H), 7.61 (d,2H), 7.71 (m,2H), 10.5 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20-29, 55, 45.6, 116.2, 130-145, 166.7, 169.3; ESI MS (*m/z*): 354.78[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub>S: C (44.13%), H (3.42%), N (19.8%).

### 2-[5-[(2-cyanopyrrolidine-1-sulfonyl)amino]-1,2,4-oxadiazol-3-yl]phenyl acetate

Yield: 84%; Melting point: 165-167°C; IR (KBr): 1455(CH<sub>2</sub>), 1560(C-H), 1600(S=O), 1690(-C=O), 2200(-C≡N), 3050(CH), 3300(NH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.80(m,6H), 2.45(m,3H), 3.8(s,1H), 7.45(d,2H), 7.77(m,2H), 10.5(s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.3, 20.9-29.3, 45.6, 55, 116.2, 123.2-151.1, 169, 166.7, 169.3; ESI MS (*m/z*): 378.08 [M+H]; Anal. Calcd. For found C<sub>15</sub>H<sub>15</sub>N<sub>5</sub>O<sub>5</sub>S: C (47.74%) H (4.01%) N (18.56%)

### N-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]-2-cyano pyrrolidine-1-sulfonamide

Yield: 79%; Melting point: 128-130°C; IR (KBr): 780(C-Br), 1100(-C=O), 1450(CH<sub>2</sub>), 1550(-S=O), 1650(-C-H), 2250(-, 1), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.80(m,6H), 3.8(d,1H), 7.38(d,2H), 7.71(d,2H), 10.5(s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 20.9, 29.3, 45.6, 45-55, 55, 116.2, 134, 125-135, 164.5-169.3; ESI MS (*m/z*): 354.78[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>BrN<sub>5</sub>O<sub>3</sub>S: C (39.13%), H (3.42%), N (19.8%).

### N-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-cyano pyrrolidine-1-sulfonamide

Yield: 72%; Melting point: 158-160°C; IR (KBr): 780(C-Cl), 1100(-C=O), 1450(CH<sub>2</sub>), 1550(-S=O), 1650(-C-H), 2250(-, 1), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40- 2.8(m,6H), 3.8 (s,1H), 7.97(d,2H), 7.48(d,2H), 10.5 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 20.9, 29.3, 45.6, 45-55, 55, 116.2, 134, 125-135, 164.5-169.3; ESI MS (*m/z*): 354.78[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub>S: C (44.13%), H (3.42%), N (19.8%).

**Table 1: Random glucose level (mg/dL) of synthesized analogs and standard drug in Streptozotocin-Nicotinamide+high-fat diet-induced diabetic rats.**

Group	Dose	1 <sup>st</sup>	7 <sup>th</sup>	14 <sup>th</sup>	21 <sup>st</sup>	28 <sup>th</sup>
Normal control	1 mL Tap water	98±3.0	95 ± 4.2	98 ±1.5	105 ±7.2	102 ± 3.2
Diabetic control	0.25% CMC	295 ± 8.2	289 ± 7.5	295 ± 8.5	275 ± 6.2	280± 4.6
Vildagliptin	10 mg/kg	280 ± 6.5 <sup>#</sup>	230 ± 8.2 <sup>#</sup>	215 ±7.2 <sup>B</sup>	205 ± 4.1 <sup>B</sup>	198 ±3.4 <sup>B</sup>
Compound B-I	100 mg/kg	287±2.36 <sup>#</sup>	235±3.1 <sup>#</sup>	222±3.62 <sup>B</sup>	215±2.20 <sup>B</sup>	212±5.67 <sup>B</sup>
Compound B-II	100 mg/kg	309±2.36 <sup>#</sup>	257±3.1 <sup>#</sup>	242±3.62 <sup>B</sup>	236±2.20 <sup>B</sup>	229±5.67 <sup>B</sup>
Compound B- III	100 mg/kg	290±2.94 <sup>#</sup>	238±3.09 <sup>#</sup>	225±3.77 <sup>B</sup>	218±5.48 <sup>B</sup>	210±4.87 <sup>B</sup>
Compound B-XI	100 mg/kg	282±5.18 <sup>#</sup>	233±2.86 <sup>#</sup>	220±4.56 <sup>B</sup>	215±3.18 <sup>B</sup>	209±2.92 <sup>B</sup>
Compound B-XIV	100 mg/kg	307±4.49 <sup>#</sup>	255±3.32 <sup>#</sup>	242±4.64 <sup>B</sup>	235±6.73 <sup>B</sup>	232±2.76 <sup>B</sup>
Compound B-XV	100 mg/kg	310±2.96 <sup>#</sup>	255±6.98 <sup>#</sup>	240±5.30 <sup>B</sup>	234±4.79 <sup>B</sup>	228±5.70 <sup>B</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscripts down the column indicate a significant difference ( $p < 0.05$ ). # means non-significant value. B means significant value.

Group	Dose	Day 1 <sup>st</sup> day	14 <sup>th</sup> day	28 <sup>th</sup> day
Normal control	0.25% CMC	61 ± 2.65	63 ± 2.70	60 ± 3.86
Diabetic control	0.25% CMC	147 ± 3.63	145 ± 4.02	149 ± 2.78 <sup>B</sup>
Vildagliptin	10 mg/kg	125 ± 2.25 <sup>#</sup>	120 ± 4.63 <sup>B</sup>	118 ± 3.38 <sup>B</sup>
B-I	100 mg/kg	125±1.05 <sup>#</sup>	120±3.39 <sup>B</sup>	117±2.36 <sup>B</sup>
B-XI	100 mg/kg	122±2.73 <sup>#</sup>	118±2.78 <sup>B</sup>	115±3.71 <sup>B</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscripts down the column indicate a significant difference ( $p < 0.05$ ). # means non-significant value. <sup>B</sup> means significant value.

Group	Dose	1 <sup>st</sup> day	14 <sup>th</sup> day	28 <sup>th</sup> day
Normal control	0.25% CMC	55 ± 5.1	57 ± 3.2	54±3.2
Diabetic control	0.25% CMC	19 ± 2.3	18 ± 3.2	17 ± 4.2
Vildagliptin	10 mg/kg	23 ± 4.1 <sup>#</sup>	38 ± 3.2 <sup>B</sup>	40 ± 4.2 <sup>B</sup>
B-I	100 mg/kg	20 ± 2.5 <sup>#</sup>	29 ± 2.3 <sup>B</sup>	32 ± 4.5 <sup>B</sup>
B-XI	100 mg/kg	22±2.6 <sup>#</sup>	31±3.1 <sup>B</sup>	34±1.6 <sup>B</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscripts down the column indicate a significant difference ( $p < 0.05$ ). # means non-significant value. <sup>B</sup> means significant value.

### N-[3-(2-bromophenyl)-1,2,4-oxadiazol-5-yl]-2-cyano pyrrolidine-1-sulfonamide

Yield: 69%; Melting point: 122-125°C; IR (KBr): 710(C-Br), 1100(-C=O), 1450(CH<sub>2</sub>), 1550(-S=O), 1650(-C-H), 2250(-, 1), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40- 2.8 (m,6H), 3.8 (s,1H), 7.97(d,2H), 8.16(m,2H), 10.5 (s,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ20.9, 29.3, 45.6, 45-55, 55, 116.2, 134, 125-135, 164.5-169.3; ESI MS ( $m/z$ ): 354.78[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>BrN<sub>5</sub>O<sub>3</sub>S: C (39.13%), H (3.42%), N (19.8%).

### 2-cyano-N-[5-(4-methyl phenyl)-1,2,4-oxadiazol-2-yl]pyrrolidine-1-sulfonamide

Yield: 74%; Melting point: 137-139°C; IR (KBr): 1050(C=O), 1450(CH<sub>2</sub>), 1550(S=O),1650(C-H), 2250(-C≡N), 3050(C-H), 2810(O-CH<sub>3</sub>), 2900(-CH<sub>3</sub>), 3050(C-H), 3450(NH); <sup>1</sup>HNMR(400 MHz,CDCl<sub>3</sub>):1.40-2.4(m,6H),3.6(S,1H),3.8(m,3H),7.03(d,1H),8.02(d,1H), 10.5(S,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 14.16-18.76, 50, 55.9, 56.5, 62.5, 123.52, 130.68, 135.85, 144.6, 166.5-169.3; ESI MS ( $m/z$ ):350.09 [M+H]; Anal. Calcd. For found C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>S: C (48.13%), H (4.33%), N (20.05%).

**Table 4: Effect of synthesized compounds on serum total cholesterol level (mg/dL) in Streptozotocin-Nicotinamide+high-fat diet-induced diabetic rats.**

Group	Dose	1 <sup>st</sup> day	14 <sup>th</sup> day	28 <sup>th</sup> day
Normal control	0.25% CMC	80 ± 3.56	85 ± 4.23	80 ± 5.32
Diabetic control	0.25% CMC	158 ± 4.45	164 ± 6.64	169 ± 5.43
Vildagliptin	10 mg/kg	145 ± 5.43 <sup>#</sup>	140 ± 5.71 <sup>B</sup>	138 ± 3.72 <sup>B</sup>
B-I	100 mg/kg	149 ± 3.41 <sup>#</sup>	143 ± 2.31 <sup>B</sup>	138 ± 1.92 <sup>B</sup>
B-XI	100 mg/kg	147 ± 2.07 <sup>#</sup>	141 ± 5.62 <sup>B</sup>	135 ± 3.58 <sup>B</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscripts down the column indicate a significant difference ( $p < 0.05$ ). <sup>#</sup> means non-significant value. <sup>B</sup> means significant value.

**Table 5: Effect of synthesized compounds on serum creatinine level (mg/dL) in Streptozotocin-Nicotinamide+high-fat diet-induced diabetic rats.**

Group	Dose	1 <sup>st</sup> day	14 <sup>th</sup> day	28 <sup>th</sup> day
Normal control	0.25% CMC	0.63 ± 0.14	0.64 ± 0.17	0.65 ± 0.25
Diabetic control	0.25% CMC	0.96 ± 0.11	1.20 ± 0.26	1.44 ± 0.20
Vildagliptin	10 mg/kg	0.97 ± 0.16 <sup>#</sup>	0.81 ± 0.34 <sup>B</sup>	0.72 ± 0.19 <sup>B</sup>
B-I	100 mg/kg	0.95 ± 0.06 <sup>#</sup>	0.81 ± 0.02 <sup>B</sup>	0.71 ± 0.12 <sup>B</sup>
B-XI	100 mg/kg	0.92 ± 0.08 <sup>#</sup>	0.78 ± 0.05 <sup>B</sup>	0.70 ± 0.06 <sup>B</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscripts down the column indicate a significant difference ( $p < 0.05$ ). <sup>#</sup> means non-significant value. <sup>B</sup> means significant value.

**Table 6: Effect of synthesized compounds on serum urea level (mg/dL) in Streptozotocin-Nicotinamide+high-fat diet.**

Group	Dose	1 <sup>st</sup> day	14 <sup>th</sup> day	28 <sup>th</sup> day
Normal control	0.25% CMC	15 ± 1.23	16 ± 1.54	15 ± 1.52
Diabetic control	0.25% CMC	22 ± 2.32	25 ± 3.41	28 ± 3.58
Vildagliptin	10 mg/kg	22 ± 4.35 <sup>#</sup>	18 ± 3.24 <sup>*</sup>	16 ± 2.76 <sup>*</sup>
B-I	100 mg/kg	21 ± 1.82 <sup>#</sup>	21 ± 1.82	18 ± 2.21 <sup>*</sup>
B-XI	100 mg/kg	22 ± 1.31 <sup>#</sup>	20 ± 2.84 <sup>*</sup>	17 ± 1.68 <sup>*</sup>

Data is presented as mean ± SD of 8 animals per group. Values with different superscript down the column indicate a significant difference ( $p < 0.05$ ). <sup>#</sup> means non-significant value. <sup>B</sup> means significant value.

### 2-cyano-N-[3-(3-methyl phenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 85%; Melting point: 145-147°C; IR (KBr): 1050(C=O), 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-C≡N), 2900(-CH<sub>3</sub>), 3050(C-H), 3450(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.08 (m, 6H), 2.34 (m, 3H), 3.8 (d, 1H), 7.1 (s, 1H), 7.35 (d, 2H), 7.97 (m, 1H), 10.58 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 21.3, 55, 46.5, 116.2, 123.1, 127.4, 126.3, 164.5-169.3; ESI MS ( $m/z$ ): 334.09 [M+H]; Anal. Calcd. For found C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>S: C (50.44%), H (4.54%), N (21.01%).

### 2-cyano-N-[3-(2-nitrophenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 81% Melting point: 192-194°C; IR (KBr): 1450(CH<sub>2</sub>); 1550(S=O), 1550(asym-NO<sub>2</sub>), 1570(asym-NO<sub>2</sub>), 1650(C-H), 2250(-16), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):

1.40-2.8 (m, 6H), 3.8 (s, 1H), 7.72 (d, 2H), 8.08 (m, 2H), 10.5 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 45.6-55, 116.2, 124.4-150.1, 150.1, 166.5-169.3; ESI MS ( $m/z$ ): 365.06 [M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>12</sub>N<sub>6</sub>O<sub>5</sub>S: C (42.86%), H (3.32%), N (23.07%).

### 2-cyano-N-[3-[4-(trifluoromethyl) phenyl]-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 87% Melting point: 137-139°C; IR (KBr): 1200CF<sub>3</sub>, 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-165), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.4-2.8 (m, 6H), 3.5 (s, 1H), 7.9 (d, 2H), 8.2 (d, 2H), 10.4 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 45.6-55, 116.2, 124.1, 125.6-131, 164.5-169.3; ESI MS ( $m/z$ ): 388.06 [M+H]; Anal. Calcd. For found C<sub>14</sub>H<sub>12</sub>F<sub>3</sub>N<sub>5</sub>O<sub>3</sub>S: C Composition: C (43.41%), H (3.12%), N (18.08%).

### 2-cyano-N-[3-(4-aminophenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 85% Melting point: 145-147°C; IR (KBr): 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-, 2253050(C-H), 3350(PrimN-H<sub>2</sub>), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.8(m,6H), 3.8(S,1H), 5.24(S,2H), 6.7(d,2H), 7.90(d,2H), 10.58(S,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 46.6-55, 116.2, 115.1-145.6, 164.5-169.3; ESI MS (*m/z*): 335.09; [M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>14</sub>N<sub>6</sub>O<sub>3</sub>S: C (46.70%), H (4.22%), N (25.14%).

### 2-cyano-N-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 75%; Melting point: 126-128°C; IR (KBr): 1250(C-O), 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-225), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.8(m,6H), 3.8(S,1H), 3.85(m,3H), 3.92(m,3H), 7.0(d,1H), 7.29(d,1H), 7.76(d,1H), 10.58(S,1H); (400 MHz, CDCl<sub>3</sub>): δ20.9-29.3, 45.6-55, 56.1, 116.2, 111-150.3, 164.5-169.3; ESI MS (*m/z*): 380.1[M+H]; Anal. Calcd. For found C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>O<sub>5</sub>S: C (47.49%) H (4.52%) N (18.46%).

### 2-cyano-N-[3-(2-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 82%; Melting point: 156-158°C; IR (KBr): 1250(C-O), 1350(O-H), 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(- 14), 3050(C-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.8(m, 6H), 3.8(s, 1H), 7.0 d, 1H), 7.06(d, 1H), 7.32(d, 1H), 7.6(d, 1H), 9.61(S, 1H), 10.58(S,1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 50, 55, 56.1, 116.2, 154.1-117.8, 164.5-169.3; ESI MS (*m/z*): 350.09[M+H]; Anal. Calcd. For found C<sub>13</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>S: C (46.56%), H (3.91%), N (20.88%).

### 2-cyano-N-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolidine-1-sulfonamide

Yield: 79%; Melting point: 112-114°C; IR (KBr): 1250(C-O); 1450(CH<sub>2</sub>), 1550(S=O), 1650(C-H), 2250(-C≡N), 3050(N-H), 3400(N-H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.40-2.8(m,6H), 3.8(S, 1H), 3.81(m, 3H), 7.29(d, 2H), 7.76(d, 2H), 10.58(S, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): 20.9-29.3, 45.6-55, 55.8, 111-150.3, 164.5-169.3; ESI MS (*m/z*): 350.09[M+H]; Anal. Calcd. For found C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>4</sub>S: C (48.13%), H (4.33%), N (20.05%).

### Evaluation of pharmacological activity

To study the anti-diabetic activity of the synthesized compounds, 72 female Albino Wistar rats were used. The animals were obtained from Animal House of National Institute of Biosciences Address: Plot no 5, Ambika C.H.S., Opp. Indraprasta Hall, Near Chaturshinghi mandir, Pune- 411016. The Modern College of Pharmacy's Institutional Animal Ethics Committee approved the study (MCP/IAEP/010/2020). In polypropylene cages at 37°C, rats were housed. Streptozotocin and nicotinamide-induced diabetic rats were used to induce diabetes in Albino Wistar rats.

### For evaluation of anti-diabetic activity

High Fat Diet Streptozotocin<sup>25</sup> and Nicotinamide-induced diabetes rats were given blood samples by retro-orbital puncture under light ether anesthesia.<sup>26,27</sup> Separation of serum was accomplished by collecting blood samples without anticoagulants. Blood samples were then centrifuged at 3500 rpm for 15 min, serum was extracted from blood and glucose is measured in the serum.<sup>28</sup> Moreover cholesterol,<sup>29</sup> triglycerides,<sup>30</sup> creatinine<sup>32</sup> and urea<sup>31</sup> levels were evaluated, respectively.

## DISCUSSION

### Chemistry

As shown in Scheme 1, we synthesized a library of sixteen title compounds (B1-B16). We have synthesized several small molecule inhibitors of DPP-IV based on using amino acids: L-proline amide. L-proline on reaction with chlorosulphonyl chloride gave 1-(chlorosulfonyl) pyrrolidine-2-carboxylic acid, which on dehydration with trifluoroacetic anhydride gave 2-cyanopyrrolidine-1-sulphonyl chloride. The compounds were all characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, ESI-MS and CHN.

### Anti-diabetic study on HFD-STZ-Nicotinamide induced diabetic rat model

Activation of inflammatory p-65 proteins and MAPKs was induced by STZ/nicotinamide in HFD rats. The anti-diabetic activity of six compounds was examined in diabetic Wistar rats induced with HFD-STZ-Nicotinamide and selected based on their molecular docking scores. Six analogs (B-I, Compound B-II, Compound B-III, Compound B-XI, Compound B-XIV, Compound B-XV) were selected based on their molecular docking scores, *in vitro* assay and were investigated for their anti-diabetic activity in induced HFD-STZ-Nicotinamide diabetic rats by using Vildagliptin as a standard drug. It is noteworthy that all the compounds displayed moderate to excellent anti-diabetic effects. Our B-I and B-XI derivatives have shown significant results in our *in vivo* models but it was lesser than standard Vildagliptin. A clear reduction in Random blood glucose level was observed from the day after treatment with B-I and B-XI (*p*<0.05) when compared to STZ-Nicotinamide and HFD induced diabetic control values (Table 1). Random blood glucose levels lowered with Vildagliptin as standard when compared with diabetic control. On 14<sup>th</sup> day (*p* < 0.05) fall was noted of total cholesterol, LDL (Table 2), HDL (Table 3), creatinine (Table 4), and urea (Table 5) in serum on the treatment of B-XI, and B-I oxadiazole derivatives. A significant increase in HDL levels in serum was observed. A normal control rat was used in this experiment.

### Structure-Activity Relationship (SAR)

An SAR study was conducted based on *in vivo* anti-hyperglycemic results of the newly developed series. These results were used to evaluate the possibility of SAR using substituents attached to the

phenyl rings of the oxadiazole scaffold. Chlorine substitution on phenyl ring at 3<sup>rd</sup> position (B-II) exhibited greater activity than hydroxy substitution at 2<sup>nd</sup> (B-XV) and 4<sup>th</sup> position (B-I). 4-hydroxy group on phenyl ring (B-I) showed more activity than 2-hydroxy group substitution on phenyl ring (B-XV). For trifluoromethyl 4<sup>th</sup> position (B-XI) showed lower activity than the 3<sup>rd</sup> position substitution of chlorine on phenyl ring (B-II). Nitro substitution on 4<sup>th</sup> position on phenyl ring (B-III) gave better activity than that of 3,4-disubstituted methyl position (B-XIV). Thus, we can say that compounds containing electron-withdrawing groups (trifluoromethyl, chlorine, nitro, hydroxy) displayed a good anti-diabetic effect.

## CONCLUSION

The ligand-binding interactions of synthesized analogs were also studied using molecular docking. *In vivo* anti-hyperglycemic activity was determined for the six selected compounds based on higher docking scores. The anti-diabetic effects of all compounds were moderate to excellent. Out of all synthesized compounds B-I and B-XI were shown significant results in our *in vivo* models but it was lesser than of standard drug. SAR developed indicated that compounds with electron-withdrawing groups as substitution on phenyl ring of oxadiazole derivatives display pronounced anti-diabetic effect as compared to compounds with electron-donating group. Compound B-XI contacting electron-withdrawing group i.e., trifluoro methyl at para position shown significant result but it is lesser than standard Vildagliptin. The oxadiazole hybrids discovered in this study seem to have the potential to become a valuable lead molecule in designing new compounds with potential anti-diabetic activity.

## ACKNOWLEDGEMENT

The authors are thankful to the management and Principal of Modern College of Pharmacy for providing infrastructure and other research facilities.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**T2D:** Type 2 diabetes; **DM:** Diabetes mellitus; **HFD:** High-fat diet; **STZ:** Streptozotocin; **DPP-IV:** Dipeptidyl peptidase-IV; **GPR40:** G-protein receptor 40; **SAR:** Structure-activity relationship; **PPAR:** Peroxisome proliferator-activated receptor; **IR:** Infrared spectroscopy; <sup>1</sup>HNMR: Hydrogen Nuclear Magnetic Resonance; <sup>13</sup>CNMR: Carbon-13 nuclear magnetic resonance; **GLP19:** Glucagon-like peptide 1; **T2DM:** Type 2 diabetes mellitus; **DPP IV:** Dipeptidyl peptidase IV; **2D:** Two-dimensional; **TLC:** Thin layer chromatography; **TMS:** Transcranial magnetic stimulation; **CDCl<sub>3</sub>:** Deuterated chloroform.

## SUMMARY

The synthesized compounds displayed dose dependent antidiabetic activity. It is noteworthy that all the compounds displayed moderate to excellent anti-diabetic effects. A clear reduction in random blood glucose level was observed from the day after treatment with B1 and B13 ( $p < 0.05$ ) when compared to STZ-Nicotinamide and HFD induced diabetic control values. Random blood glucose levels lowered with Vildagliptin as standard when compared with diabetic control. On 14<sup>th</sup> day ( $p < 0.05$ ) fall was noted of total cholesterol, LDL, creatinine and urea in serum on the treatment of B1, and B13 oxadiazole derivatives. Whereas a significant rise in HDL in serum was observed. For this experiment, a normal control rat was used for control.

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**Cite this article:** Salve MTJ. Synthesis of Cyclopyrrolidine Clubbed with Oxadiazole Bases and Evaluation of their Anti-Diabetic Activity through *in vivo* Model. *Indian J of Pharmaceutical Education and Research.* 2023;57(3s):s749-s757.