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Synthesis and evaluation of some 2-((benzothiazol-2-ylthio) methyl)-5-phenyl-1, 3, 4-oxadiazole derivatives as antidiabetic agents

Sunil Kumar[1,2*], D S Rathore[1], Gopal Garg[1], Kapil Khatri[2], Rahul Saxena[1], Sanjeev K. Sahu[3]

[1]NIMS Institute of Pharmacy, NIMS University, Jaipur (Rajasthan) India
[2]Ravishankar College of Pharmacy, Bhopal (M.P.) India
[3]Oriental College of Pharmacy, Bhopal (M.P.) India

ABSTRACT

Some of derivatives containing oxadiazole and benzothiazole moieties 6(a-l) were synthesized and the structure of synthesized compounds was elucidated by IR, ^{1}HNMR, ^{13}C NMR and mass spectroscopy. This research article deals with newly synthesized benzothiazole containing oxadiazole derivatives that were assayed for investigation of their *in vivo* hypoglycemic activity by alloxan induced diabetic model in rat. All these derivatives showed significant biological efficacy when compared to a potent and well known antidiabetic agent (i.e. Glibenclamide). All the compounds were effective, amongst them 6f showed more prominent activity at 350 mg/kg p.o. The experimental results are statistically significant at $p<0.01$ and $p<0.05$ level.

Key words: Diabetes, Substituted benzthiazole derivatives, Oxadiazole, Hypoglycemic activity, Alloxan induced diabetic model

Introduction

Diabetes is one of metabolic disorders in the world characterized by persistent hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. It is considered as one of the five leading causes of death in the world. The World Health Organization (WHO) estimates that more than 220 million people worldwide have diabetes and this number is likely to more than double by 2030 (WHO, 2009). Several drugs such as sulfonylurea and biguanides are presently available to reduce hyperglycemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is crucial to overcome these problems. Heterocyclic compounds are the mainstay of antidiabetic therapy for many years [1].

**Correspondence*
Dr. Sunil Kumar
NIMS Institute of Pharmacy, NIMS University, Jaipur (Rajasthan) India
E Mail: yagnikvns@gmail.com

In current years heterocyclic analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of diabetes [2-3]. 2-mercaptobenzothiazole derivatives are known to possess various pharmacological activities [4]. Benzothiazole ring system is present in various marine and terrestrial natural compounds, which have useful biological activities[5].The benzthiazole derivatives has been play vital role in biological fields such as antitumor, antitubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antifungal, a topical carbonic anhydrase inhibitor and an antihypoxic. Benzothiazole derivatives containing benzimidazole and imidazoline ring have diverse chemical reactivity along with broad spectrum of biological activity which are valuable for its great pharmaceutical [6-8]. All these literatures deal with significant interest to synthesize the benzothiazole derivatives with an aim to obtain potent biologically active and safe anti diabetic agents.

Material and methods

All the chemicals were of synthetic grade and commercially procured from Himedia Chemicals, Mumbai (Maharashtra) INDIA. Melting points were determined on a Tempo capillary melting point apparatus in open capillary tube and are uncorrected. All FTIR spectra were recorded (vmax in cm^{-1}) on Bruker Tensor 27 FT-IR spectrometer. ^{1}H-NMR (proton nuclear magnetic resonance) spectrum were recorded at 300 MHz, after dissolving in a suitable solvent (DMSO,$CDCl_3$ or D_2O) on Bruker Avance II 400 MHz, USA FT-NMR spectrometer using tetramethylsilane as internal standard and chemical shifts (δ) are reported in parts per million (ppm). ^{13}C NMR was also recorded on Bruker Avance II FT-NMR spectrometer at frequency of 100 MHz. The spin multiplicities are indicated by symbols, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were recorded on Waters UPLC-TQD Mass spectrometer using electrospray ionization (ESI) technique**.** The purity of the compounds was ascertained by thin layer chromatography (TLC) and elemental analysis. Plates for TLC were prepared with silica gel G and activated at 110 ^{0}C for 30 min. Iodine vapors was used to develop the TLC plates. Elemental analyses were performed on a Vario EL-III analyzer.

General Method of Synthesis for Benzthiazole Derivatives

All the compounds were synthesized by using a synthetic route given in Fig 1:

Table 1: Benzothiazole derivatives with different substitutions

S.NO.	Compound Code	R_1	R_2	R_3
1.	6a	CH_3	H	C_6H_{5-}
2.	6b	CH_3	H	$pNH_2C_6H_{4-}$
3.	6c	CH_3	H	$pNO_2C_6H_{4-}$
4.	6d	CH_3	H	$pOCH_3C_6H_{4-}$
5.	6e	NO_2	H	C_6H_{5-}
6.	6f	NO_2	H	$pNH_2C_6H_{4-}$
7.	6g	NO_2	H	$pNO_2C_6H_{4-}$
8.	6h	NO_2	H	$pOCH_3C_6H_{4-}$
9.	6i	H	NO_2	C_6H_{5-}
10.	6j	H	NO_2	$pNH_2C_6H_{4-}$
11.	6k	H	NO_2	$pNO_2C_6H_{4-}$
12.	6l	H	NO_2	$pOCH_3C_6H_{4-}$

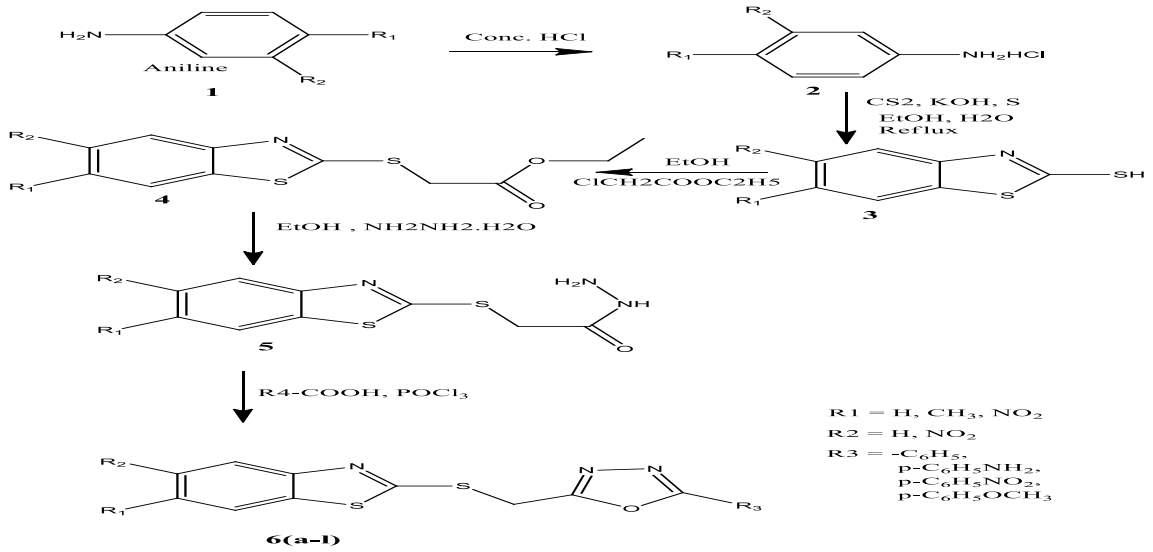

Fig 1: Scheme of Synthesis for Benzothiazole Derivatives

***Synthesis of Substitutes Aniline Hydrochloride Salt* [2]:** The aniline (0.1mol) was taken in a round bottom flask and added a mixture of HCl (9ml) & water (25ml) .Then solution was heated for about 30min and cool at room temp. Further, ammonium thiocyanate (0.1mol) was added to reaction mixture, refluxed for 4 hrs and cool it .The precipitate was filtered, washed with water, dried and crystallized from ethanol.

***Synthesis of Substituted 2-Mercaptobenzothiazole* [3]:** A mixture of compound **2** (0.0025 mol), Potassium hydroxide (0.75gm) in water (6 ml) and carbon disulphide (1.6 g, 0.01 mol) in presence of sulphur (5ml) and absolute ethanol (30 mL) at 280-285^{0}c was heated under reflux for 2 h. and 600-700 psi pressure. The reaction mixture was cooled, filtered and the filtrate was acidified with dilute hydrochloric acid, the product formed was collected and recrystallized from ethanol [9].

***Synthesis of Substituted ethyl 2-(benzo[d]thiazol-2-ylthio)acetate*[4]:**2Mercaptobenzothiazole(0.2mol) and ethylchloroacetate (0.02 mol) in dry acetone in the presence of K2CO3 (20g) was refluxed for 10 hr and the reaction mixture poured into ice and neutralized with dil.HCl, the solid thus obtained was washed several times with water and recrystallized from chloroform.

***Synthesis of Substituted 2-(benzo[d]thiazol-2-ylthio)acetohydrazide* [5]:**In to a clean dry 100 mL round bottomed flask, the compound 4 **(**0.01 mol) was dissolved in ethanol (60 mL). The hydrazine hydrate (0.02 mol) (99%) was added drop by drop with constant stirring and the content were refluxed for 8 h, cooled to room temperature.

Synthesis of Substituted 2-((benzo[d]thiazol-2-ylthio)methyl)-5-phenyl-1,3,4-oxadiazole Derivatives [6a-l]:A mixture of compound **5** (1 g, 0.01 mol) and different aryl acids (0.02 mol) in phosphoryl chloride (10 mL) was refluxed for 5 h. The resultant mixture was cooled to room temperature and poured into crushed ice with stirring. The solid thus obtained was filtered, washed with water and crystallized from ethanol to give compounds [10].

Determination of Physical Characteristic Properties of Synthesized Derivatives

All physical characteristic properties were determined for all the synthesized derivatives that include molecular formula, molecular weight, melting point, percentage yield and Rf value.

Pharmacological Evaluation of Synthesized Derivatives

Determination of acute toxicity [11]

The acute toxicity of synthesized benzothiazole derivatives were determined by using female albino rats (20–25 g) which were maintained under the standard conditions. The acclimatized animals (n= 5) were kept fasting with water *ad libitum* for 12 h prior to the experiment. The animals were administered with single dose of test compounds at a dose of 2000 mg/kg and observed for their mortality during 14 days period for toxicity study. The doses were increased up to 1000 mg/kg and rats were observed up to 02 weeks for their behavioural, economical and neurological profiles except slight depression in their activity. No such signs, symptoms and mortality were observed even after 14 days. Hence the LD50 cut off value of the test compounds was fixed at 350 mg/kg and the same dose was considered for evaluation of anti diabetic activity. All the animal experiments were conducted by the approval of Institutional Animal Ethics Committee, Sapience Bio-analytical Laboratory Bhopal, Madhya Pradesh, India

Assessments of anti-diabetic activity in alloxan-induced diabetic rats [12]

Induction of experimental diabetes by Alloxan monohydrate

The fresh solution of Alloxan monohydrate in normal saline was administered p.o. into fasted rats at a dose of 120 mg/kg body wt. After alloxan administration (i.p.), rats were given 5% (w/v) dextrose solution in feeding bottles for next 24 h in their cages to to prevent hypoglycaemia. The animals showing blood glucose range of 200-400 mg dL^{-1} were used for the experiment and the hyperglycemia was confirmed after 72 hours of Alloxan monohydrate administration (i.p.). The animals were also observed for consistent hyperglycaemia (fasting blood glucose) between 200-400 mg/dl up to 14 days.

Experimental Design

Animals were divided into fifteen groups of 6 animals in each (n=6). Group 1 Non diabetic animals received normal saline solution as normal control group; Group 2 diabetic animals received 1 ml of 0.5% carboxy methyl cellulose as positive diabetic control group; Group 3 diabetic animals received Glibenclamide 20 mg/kg as standard group; Groups (4-15) diabetic animals received compounds 6a-6l in a single dose of 350 mg/kg body weight p.o. respectively for 14 days continuously.

Blood Glucose Measurement

Blood glucose level was monitored by tail dipping method. The blood sample was dropped on the dextrostrix reagent pad. The strip was inserted into microprocessor digital blood glucometer and reading ware noted. The blood glucose level was monitored at 0 hr, 7hr, 14hr, 21hr respectively.

Statistical Analysis

The values were expressed as mean ± S.E.M. Data were analyzed using One-way ANOVA followed by Tukey-Kramer test. The values were considered to be significant at $p<0.05$ and $p<0.01$ level.

Results

All the benzthiazole derivatives 6(a-l) were synthesized by the given scheme and reaction process was monitored by thin layer chromatography method using silica gel-G stationary phase, ethyl acetate: chloform (2:1) as mobile phase, and detecting the spots with iodine vapors. All the physical constant data were characterized for all the synthesized derivatives that are given in the Table 2.

Table 2: Physical Constant Data of Synthesized Derivatives

Properties / Code of Derivatives	Mol. Formula	Mol. Wt.	M.P. in ^{0}C	% Yield	Rf
6a	$C_{17}H_{13}N_3OS_2$	339.43	197-199	62.3	0.58
6b	$C_{17}H_{14}N_4OS_2$	354.45	214-216	72.5	0.62
6c	$C_{17}H_{12}N_4O_3S_2$	384.43	203-205	75.9	0.74
6d	$C_{18}H_{15}N_3O_2S_2$	369.46	265-268	66.8	0.69
6e	$C_{16}H_{10}N_4O_3S_2$	370.41	187-189	68.8	0.65
6f	$C_{16}H_{11}N_5O_3S_2$	385.42	208-210	79.1	0.71
6g	$C_{16}H_9N_5O_5S_2$	415.40	190-192	83.2	0.81
6h	$C_{17}H_{12}N_4O_4S_2$	400.43	231-233	73.7	0.78
6i	$C_{16}H_{10}N_4O_3S_2$	370.41	166-168	58.4	0.61
6j	$C_{16}H_{11}N_5O_3S_2$	385.42	183-185	64.7	0.67
6k	$C_{16}H_9N_5O_5S_2$	415.40	173-175	71.2	0.77
6l	$C_{17}H_{12}N_4O_4S_2$	400.43	220-225	60.9	0.71

Experimental Data of Synthesized Derivatives

(A) 2-(((6-methylbenzo[d]thiazol-2-yl)thio)methyl) -5-phenyl-1,3,4-oxadiazole[compound6a]:

Yield: 62.3 %; M.P. 197- 199 ^{0}C; Anal. Cal. for $C_{17}H_{13}N_3OS_2$: C, 60.15; H, 3.86; N, 12.38; O, 4.71; S, 18.89 %; found: C, 60.18; H, 3.82; N, 12.36; O, 4.73; S, 18.90 %; FT-IR (νmax): 3058 (Aromatic C-H strech.), 2963(Asym. aliphatic C-H strech.), 2861 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1619 (C=N stretch.), 1602 (Phenyl ring stretch.), 1512 (Phenyl C-H out of plane bending), 1467 (CH_2 bending), 1458 (Asym CH_3 bending), 1392 (Sym. CH_3 bending), 1278 (C-N Strech), 1154 (C-O stretch.), 758 & 712 (loop for mono substitution at phenyl ring), 694 (C-S stretch) cm^{-1};^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.09-8.07 (d, 2H phenyl ring protons at C_2 & C_6), 7.89-7.87 (d, 1H benzthiazole ring proton at C_8), 7.81 (s, 1H benzthiazole ring proton at C_5), 7.55-7.51 (t, 2H phenyl ring protons at C_3 & C_5), 7.42-7.40 (t, 1H phenyl ring proton at C_4), 7.33-7.31 (d, 1H benzthiazole ring proton at C_7), 4.54 (s, 2H, S$C\underline{H}_2$- at oxadiazole ring), 2.34 (s, 3H, $C\underline{H}_3$ at benzthiazole ring);^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.7 (C_2 carbon at benzthiazole ring), 164.5 (oxadiazole ring carbon at phenyl linkage), 163.2 (oxadiazole ring carbon at thiomethyl linkage), 150.4 (C_9 carbon at benzthiazole ring), 135.2 (C_4 carbon at benzthiazole ring), 134.2 (C_6 carbon at benzthiazole ring), 129.2 (C_3 & C_5 carbons at phenyl ring), 128.7 (C_4 carbon at phenyl ring), 127.5 (C_2 & C_6 carbons at phenyl ring), 126.6 (C_7 carbon at benzthiazole ring), 121.5 (C_8 carbon at benzthiazole ring),122.9 (C_1 carbon at phenyl ring), 121.3 (C_5 carbon at benzthiazole ring), 34.8 (-S$C\underline{H}_2$- carbon at oxadiazole ring), 20.9 (methyl carbon at benzthiazole ring); m/e (ESI): 339 (M^+).

(B) 4-(5-(((6-methylbenzo[d]thiazol-2-yl)thio) methyl)-1,3,4-oxadiazol-2-yl)aniline [compound 6b]:

Yield: 72.5 %; M.P. 214- 216 ^{0}C; Anal. Cal. for $C_{17}H_{14}N_4OS_2$: C, 57.61; H, 3.98; N, 15.81; O, 4.51; S, 18.09 %; found C, 57.63; H, 3.94; N, 15.79; O, 4.54; S, 18.10%; FT-IR (νmax): 3412 (Asym. N-H strech.), 3343(Sym. N-H strech.), 3045 (Aromatic C-H strech.), 2959 (Asym. aliphatic C-H strech.), 2857 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1618 (C=N stretch.), 1598 (Phenyl ring stretch.), 1509 (Phenyl C-H out of plane bending), 1465 (CH_2 bending), 1456 (Asym CH_3 bending), 1390 (Sym. CH_3 bending), 1275 (C-N Strech), 1158 (C-O stretch.), 868 (loop for di substitution at phenyl ring), 798 (out of plan N-H bending), 697 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 7.89-7.87 (d, 1H benzthiazole ring proton at C_8), 7.81 (s, 1H benzthiazole ring proton at C_5), 7.54-7.52 (d, 2H phenyl ring protons at C_2 & C_6), 7.33-7.31 (d, 1H benzthiazole ring proton at C_7), 7.60-7.58 (d, 2H phenyl ring protons at C_3 & C_5), 6.27 (s, 2H, Ph-N$\underline{H}_2$), 4.54 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring), 2.34 (s, 3H, C$\underline{H}_3$ at benzthiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.6 (C_2 carbon at benzthiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 163.4 (oxadiazole ring carbon at thiomethyl linkage), 150.6 (C_9 carbon at benzthiazole ring), 145.6 (C_4 carbon at phenyl ring), 135.7 (C_4 carbon at benzthiazole ring), 134.8 (C_6 carbon at benzthiazole ring), 128.3 (C_2 & C_6 carbons at phenyl ring), 126.9 (C_7 carbon at benzthiazole ring), 121.9 (C_8 carbon at benzthiazole ring), 121.6 (C_5 carbon at benzthiazole ring), 116.7 (C_1 carbon at phenyl ring), 115.1 (C_3 & C_5 carbons at phenyl ring), 35.2 (-S$\underline{C}H_2$- carbon at oxadiazole ring), 21.3 (methyl carbon at benzthiazole ring); m/e (ESI): 354 (M^+).

(C) 2-(((6-methylbenzo[d]thiazol-2-yl)thio) methyl) -5-(4-nitrophenyl)-1,3,4-oxadiazole [compound 6c]:

Yield: 75.9 %; M.P. 203- 205 ^{0}C; Anal. Cal. for $C_{17}H_{12}N_4O_3S_2$: C, 53.11; H, 3.15; N, 14.57; O, 12.49; S, 16.68 %; found: C, 53.13; H, 3.17; N, 14.53; O, 12.51; S, 16.66 %; FT-IR (νmax): 3045 (Aromatic C-H strech.), 2959 (Asym. aliphatic C-H strech.), 2857 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1618 (C=N stretch.), 1598 (Phenyl ring stretch.), 1552 (Asym. N=O stretch.), 1509 (Phenyl C-H out of plane bending), 1465 (CH_2 bending), 1456 (Asym CH_3 bending), 1390 (Sym. CH_3 bending), 1349 (Sym. N=O stretch.), 1275 (C-N Strech), 1158 (C-O stretch.), 872 (loop for di substitution at phenyl ring), 696 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.33-8.32 (d, 2H phenyl ring protons at C_3 & C_5), 7.25-7.23 (d, 2H phenyl ring protons at C_2 & C_6), 7.89-7.87 (d, 1H benzthiazole ring proton at C_8), 7.81 (s, 1H benzthiazole ring proton at C_5), 7.33-7.31 (d, 1H benzthiazole ring proton at C_7), 4.54 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring), 2.34 (s, 3H, C$\underline{H}_3$ at benzthiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.5 (C_2 carbon at benzthiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 163.4 (oxadiazole ring carbon at thiomethyl linkage), 150.4 (C_9 carbon at benzthiazole ring), 147.9 (C_4 carbon at phenyl ring), 135.3 (C_4 carbon at benzthiazole ring), 134.5 (C_6 carbon at benzthiazole ring), 132.2 (C_1 carbon at phenyl ring), 130.9 (C_2 & C_6 carbons at phenyl ring), 128.8 (C_3 & C_5 carbons at phenyl ring),126.6 (C_7 carbon at benzthiazole ring), 121.5 (C_8 carbon at benzthiazole ring), 121.8 (C_5 carbon at benzthiazole ring), 35.4 (-S$\underline{C}H_2$- carbon at oxadiazole ring), 21.5 (methyl carbon at benzthiazole ring); m/e (ESI): 384 (M^+).

(D) 2-(4-methoxyphenyl)-5-(((6 methylbenzo [d] thiazol-2-yl)thio)methyl)-1,3,4-oxadiazole [compound 6d]:

Yield: 66.8 %; M.P. 265-268 ^{0}C; Anal. Cal. for $C_{18}H_{15}N_3O_2S_2$: C, 58.52; H, 4.09; N, 11.37; O, 8.66; S, 17.36 %; found: C, 58.54; H, 4.11; N, 11.34; O, 8.68; S, 17.33 %; FT-IR (νmax): 3048 (Aromatic C-H strech.), 2962 (Asym. aliphatic C-H strech.), 2859 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1617 (C=N stretch.), 1601 (Phenyl ring stretch.), 1511 (Phenyl C-H out of plane bending), 1467 (CH_2 bending), 1459 (Asym CH_3 bending), 1388 (Sym. CH_3 bending), 1277 (C-N Strech), 1246 (methoxy Asym. C-O strech), 1155 (oxadiazole ring C-O stretch.), 1038 (methoxy sym. C-O strech), 870 (loop for di substitution at phenyl ring), 697 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.09-8.07 (d, 2H phenyl ring protons at C_2 & C_6), 7.89-7.87 (d, 1H benzthiazole ring proton at C_8), 7.81 (s, 1H benzthiazole ring proton at C_5), 7.33-7.31 (d, 1H benzthiazole ring proton at C_7), 7.06-7.05 (d, 2H phenyl ring protons at C_3 & C_5),4.54 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring), 3.83 (s, 3H, Ph-OC$\underline{H}_3$), 2.34 (s, 3H, C$\underline{H}_3$ at benzthiazole ring);^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.8 (C_2 carbon at benzthiazole ring), 164.6 (oxadiazole ring carbon at phenyl linkage), 163.4 (oxadiazole ring carbon at thiomethyl linkage), 160.6 (C_4 carbon at phenyl ring), 150.9 (C_9 carbon at benzthiazole ring), 135.4 (C_4 carbon at benzthiazole ring), 134.3 (C_6 carbon at benzthiazole ring), 126.6 (C_7 carbon at benzthiazole ring), 121.5 (C_8 carbon at benzthiazole ring), 121.9 (C_5 carbon at benzthiazole ring), 118.4 (C_1 carbon at phenyl ring), 115.9 (C_2 & C_6 carbons at phenyl ring), 114.8 (C_3 & C_5 carbons at phenyl ring), 55.8 (methoxy carbons at phenyl ring), 35.4 (-S$\underline{C}H_2$- carbon at oxadiazole ring), 21.5 (methyl carbon at benzthiazole ring); m/e (ESI): 369 (M^+).

(E) 2-(((6-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole [compound 6e]:

Yield: 68.8 %; M.P. 187- 189 ^{0}C; Anal. Cal. for $C_{16}H_{10}N_4O_3S_2$: C, 51.88; H, 2.72; N, 15.13; O, 12.96; S, 17.31%; found: C, 51.86; H, 2.70; N, 15.16; O, 12.98; S, 17.30%; FT-IR (νmax): 3061 (Aromatic C-H strech.), 2932(Asym. aliphatic C-H strech.), 2857 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1615 (C=N stretch.), 1597 (Phenyl ring stretch.), 1548 (Asym. N=O stretch.), 1508 (Phenyl C-H out of plane bending), 1466 (CH_2 bending), 1353 (Sym. N=O stretch.), 1281 (C-N Strech), 1158 (C-O stretch.), 754 & 714 (loop for mono substitution at phenyl ring), 696 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.61 (s, 1H benzthiazole ring proton at C_5), 8.32-8.30 (d, 1H benzthiazole ring proton at C_7), 8.07-8.05 (d, 1H benzthiazole ring proton at C_8), 8.02-8.00 (d, 2H phenyl ring protons at C_2 & C_6), 7.55-7.51 (t, 2H phenyl ring protons at C_3 & C_5), 7.44-7.42 (t, 1H phenyl ring proton at C_4), 4.54 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.5 (C_2 carbon at benzthiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 163.1(oxadiazole ring carbon at thiomethyl linkage), 159.6 (C_9 carbon at benzthiazole ring), 143.3 (C_6 carbon at benzthiazole ring), 136.0 (C_4 carbon at benzthiazole ring), 129.4 (C_3 & C_5 carbons at phenyl ring), 128.5 (C_4 carbon at phenyl ring), 127.7 (C_2 & C_6 carbons at phenyl ring), 122.8 (C_1 carbon at phenyl ring), 122.4 (C_8 carbon at benzthiazole ring), 121.3 (C_7 carbon at benzthiazole ring), 119.1 (C_5 carbon at benzthiazole ring), 34.6 (-S$\underline{C}H_2$- carbon at oxadiazole ring); m/e (ESI): 370 (M^+).

(F) 4-(5-(((6-methylbenzo[d]thiazol-2-yl)thio) methyl)-1,3,4-oxadiazol-2-yl)aniline [compound 6f]:

Yield: 79.1 %; M.P. 208- 210 ^{0}C; Anal. Cal. for $C_{16}H_{11}N_5O_3S_2$: C, 49.86; H, 2.88; N, 18.17; O, 12.45; S, 16.64 %; found: C, 49.89; H, 2.84; N, 18.19; O, 12.43; S, 16.61 %; FT-IR (νmax): 3415 (Asym. N-H strech.), 3346(Sym. N-H strech.), 3048 (Aromatic C-H strech.), 2929 (Asym. aliphatic C-H strech.), 2856 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1617 (C=N stretch.), 1601 (Phenyl ring stretch.), 1513 (Phenyl C-H out of plane bending), 1467 (CH_2 bending), 1277 (C-N Strech), 1162 (C-O stretch.), 872 (loop for di substitution at phenyl ring), 802 (out of plan N-H bending), 695 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.62 (s, 1H benzthiazole ring proton at C_5), 8.32-8.30 (d, 1H benzthiazole ring proton at C_7), 8.01-8.00 (d, 1H benzthiazole ring proton at C_8), 7.54-7.52 (d, 2H phenyl ring protons at C_2 & C_6), 6.57-6.55 (d, 2H phenyl ring protons at C_3 & C_5), 6.27 (s, 2H, Ph-N$\underline{H}_2$), 4.55 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.6 (C_2 carbon at benzthiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 163.2 (oxadiazole ring carbon at thiomethyl linkage), 159.4(C_9 carbon at benzthiazole ring), 145.4 (C_4 carbon at phenyl ring), 143.5 (C_6 carbon at benzthiazole ring), 136.2 (C_4 carbon at benzthiazole ring), 128.5 (C_2 & C_6 carbons at phenyl ring), 122.6 (C_8 carbon at benzthiazole ring), 121.5 (C_7 carbon at benzthiazole ring), 119.3 (C_5 carbon at benzthiazole ring), 116.3 (C_1 carbon at phenyl ring), 115.3 (C_3 & C_5 carbons at phenyl ring), 34.7 (-S$\underline{C}H_2$- carbon at oxadiazole ring); m/e (ESI): 385 (M^+).

(G) 2-(((6-nitrobenzo[d]thiazol-2-yl)thio) meth yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole [compound 6g]:

Yield: 83.2 %; M.P. 190- 192 ^{0}C; Anal. Cal. for $C_{16}H_9N_5O_5S_2$: C, 46.26; H, 2.18; N, 16.86; O, 19.26; S, 15.44 %; found: C, 46.24; H, 2.14; N, 16.89; O, 19.28; S, 15.45 %; FT-IR (νmax): 3049 (Aromatic C-H strech.), 2929 (Asym. aliphatic C-H strech.), 2861 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1617 (C=N stretch.), 1602 (Phenyl ring stretch.), 1548 (Asym. N=O stretch.), 1510 (Phenyl C-H out of plane bending), 1468 (CH_2 bending), 1354 (Sym. N=O stretch.), 1279 (C-N Strech), 1156 (C-O stretch.), 876 (loop for di substitution at phenyl ring), 694 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.62 (s, 1H benzthiazole ring proton at C_5), 8.38-8.36 (d, 2H phenyl ring protons at C_3 & C_5), 8.32-8.30 (d, 1H benzthiazole ring proton at C_7), 8.24-8.22 (d, 2H phenyl ring protons at C_2 & C_6), 8.01-8.00 (d, 1H benzthiazole ring proton at C_8), 4.55 (s, 2H, -SC$\underline{H}_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.8 (C_2 carbon at benzthiazole ring), 164.6 (oxadiazole ring carbon at phenyl linkage), 163.5 (oxadiazole ring carbon at thiomethyl linkage), 159.6(C_9 carbon at benzthiazole ring), 147.7 (C_4 carbon at phenyl ring), 143.7 (C_6 carbon at benzthiazole ring), 136.5 (C_4 carbon at benzthiazole ring), 132.4 (C_1 carbon at phenyl ring), 130.6 (C_2 & C_6 carbons at phenyl ring), 128.5 (C_3 & C_5 carbons at phenyl ring), 122.9 (C_8 carbon at benzthiazole ring), 121.7 (C_7 carbon at benzthiazole ring), 119.6 (C_5 carbon at benzthiazole ring), 34.9 (-S$\underline{C}H_2$- carbon at oxadiazole ring); m/e (ESI): 415 (M^+).

(H) 2-(4-methoxyphenyl)-5-(((6-nitrobenzo [d]thia zol-2-yl)thio)methyl)-1,3,4-oxadiazole[compound 6h]: Yield: 73.7 %; M.P. 231-233 ^{0}C; Anal. Cal. for $C_{17}H_{12}N_4O_4S_2$: C, 50.99; H, 3.02; N, 13.99; O, 15.98; S, 16.02 %; found: C, 51.02; H, 3.01; N, 13.94; O,

16.00; S, 16.03 %; FT-IR (νmax): 3055 (Aromatic C-H strech.), 2958 (Asym. aliphatic C-H strech.), 2864 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1615 (C=N stretch.), 1603 (Phenyl ring stretch.), 1552(Asym. N=O stretch.), 1514 (Phenyl C-H out of plane bending), 1469 (CH_2 bending), 1457 (Asym CH_3 bending), 1386 (Sym. CH_3 bending), 1354 (Sym. N=O stretch.), 1275 (C-N Strech), 1249 (methoxy Asym. C-O strech), 1158 (oxadiazole ring C-O stretch.), 1039 (methoxy sym. C-O strech), 873 (loop for di substitution at phenyl ring), 695 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 8.62 (s, 1H benzthiazole ring proton at C_5), 8.32-8.30 (d, 1H benzthiazole ring proton at C_7), 8.04-8.02 (d, 2H phenyl ring protons at C_2 & C_6), 8.01-8.00 (d, 1H benzthiazole ring proton at C_8), 7.03-7.01 (d, 2H phenyl ring protons at C_3 & C_5), 4.55 (s, 2H, -SC<u>H</u>$_2$- at oxadiazole ring), 3.85 (s, 3H, Ph-OC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.5 (C_2 carbon at benzthiazole ring), 164.4 (oxadiazole ring carbon at phenyl linkage), 163.3 (oxadiazole ring carbon at thiomethyl linkage), 160.8 (C_4 carbon at phenyl ring), 159.3(C_9 carbon at benzthiazole ring), 143.4 (C_6 carbon at benzthiazole ring), 136.2 (C_4 carbon at benzthiazole ring), 122.7 (C_8 carbon at benzthiazole ring), 121.5 (C_7 carbon at benzthiazole ring), 119.9 (C_5 carbon at benzthiazole ring), 118.3 (C_1 carbon at phenyl ring), 115.6 (C_2 & C_6 carbons at phenyl ring), 114.5 (C_3 & C_5 carbons at phenyl ring), 34.6 (-S<u>C</u>H$_2$- carbon at oxadiazole ring); m/e (ESI): 400 (M^+).

(I) 2-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole [compound 6i]: Yield: 58.4 %; M.P. 166- 168 ^{0}C; Anal. Cal. for $C_{16}H_{10}N_4O_3S_2$: C, 51.88; H, 2.72; N, 15.13; O, 12.96; S, 17.31 %; found: C, 51.90; H, 2.68; N, 15.11; O, 12.98; S, 17.33 %; FT-IR (νmax): 3064 (Aromatic C-H strech.), 2935(Asym. aliphatic C-H strech.), 2859 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1617 (C=N stretch.), 1599 (Phenyl ring stretch.), 1546 (Asym. N=O stretch.), 1510 (Phenyl C-H out of plane bending), 1468 (CH_2 bending), 1357 (Sym. N=O stretch.), 1277 (C-N Strech), 1155 (C-O stretch.), 757 & 717 (loop for mono substitution at phenyl ring), 698 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 9.16 (s, 1H benzthiazole ring proton at C_8), 8.32-8.30 (d, 1H benzthiazole ring proton at C_6), 8.27-8.25 (d, 1H benzthiazole ring proton at C_5), 8.04-8.02 (d, 2H phenyl ring protons at C_2 & C_6), 7.54-7.51 (t, 2H phenyl ring protons at C_3 & C_5), 7.42-7.40 (t, 1H phenyl ring proton at C_4), 4.53 (s, 2H, -SC<u>H</u>$_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.6 (C_2 carbon at benzthiazole ring), 164.2 (oxadiazole ring carbon at phenyl linkage), 163.3(oxadiazole ring carbon at thiomethyl linkage), 154.4 (C_9 carbon at benzthiazole ring), 146.3 (C_7 carbon at benzthiazole ring), 141.1 (C_4 carbon at benzthiazole ring), 129.6 (C_3 & C_5 carbons at phenyl ring), 128.3 (C_4 carbon at phenyl ring), 127.4 (C_2 & C_6 carbons at phenyl ring), 122.9 (C_1 carbon at phenyl ring), 122.4 (C_5 carbon at benzthiazole ring), 119.3 (C_6 carbon at benzthiazole ring), 117.4 (C_8 carbon at benzthiazole ring), 34.7 (-S<u>C</u>H$_2$- carbon at oxadiazole ring); m/e (ESI): 370 (M^+).

(J) 4-(5-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazol-2-yl)aniline [compound 6j]: Yield: 64.7 %; M.P. 183-85 ^{0}C; Anal. Cal. for $C_{16}H_{11}N_5O_3S_2$: C, 49.86; H, 2.88; N, 18.17; O, 12.45; S, 16.64 %; found: C, 49.88; H, 2.85; N, 18.15; O, 12.47; S, 16.65%; FT-IR (νmax): 3418 (Asym. N-H strech.), 3348 (Sym. N-H strech.), 3053 (Aromatic C-H strech.), 2933 (Asym. aliphatic C-H strech.), 2858 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1615 (C=N stretch.), 1603 (Phenyl ring stretch.), 1511 (Phenyl C-H out of plane bending), 1465 (CH_2 bending), 1279 (C-N Strech), 1164 (C-O stretch.), 874 (loop for di substitution at phenyl ring), 798 (out of plan N-H bending), 697 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 9.16 (s, 1H benzthiazole ring proton at C_8), 8.32-8.30 (d, 1H benzthiazole ring proton at C_6), 8.27-8.25 (d, 1H benzthiazole ring proton at C_5), 7.54-7.52 (d, 2H phenyl ring protons at C_2 & C_6), 6.55-6.54 (d, 2H phenyl ring protons at C_3 & C_5), 6.28 (s, 2H, Ph-N<u>H</u>$_2$), 4.53 (s, 2H, -SC<u>H</u>$_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.7 (C_2 carbon at benzthiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 163.5(oxadiazole ring carbon at thiomethyl linkage), 154.6 (C_9 carbon at benzthiazole ring), 146.5 (C_7 carbon at benzthiazole ring), 145.5 (C_4 carbon at phenyl ring), 141.3 (C_4 carbon at benzthiazole ring), 128.6 (C_2 & C_6 carbons at phenyl ring), 122.6 (C_5 carbon at benzthiazole ring), 119.5 (C_6 carbon at benzthiazole ring), 117.6 (C_8 carbon at benzthiazole ring), 116.4 (C_1 carbon at phenyl ring), 115.4 (C_3 & C_5 carbons at phenyl ring), 34.5 (-S<u>C</u>H$_2$- carbon at oxadiazole ring); m/e (ESI): 385 (M^+).

(K) 2-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole [compound 6k]: Yield: 71.2 %; M.P. 173- 175 ^{0}C; Anal. Cal. for $C_{16}H_9N_5O_5S_2$: C, 46.26; H, 2.18; N, 16.86; O, 19.26; S, 15.44 %; found: C, 46.29; H, 2.15; N, 16.82; O, 19.29; S, 15.45 %; FT-IR (νmax): 3053 (Aromatic C-H strech.), 2933 (Asym. aliphatic C-H strech.), 2858 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1616 (C=N stretch.),

1604 (Phenyl ring stretch.), 1553 (Asym. N=O stretch.), 1512 (Phenyl C-H out of plane bending), 1466 (CH_2 bending), 1356 (Sym. N=O stretch.), 1276 (C-N Strech), 1154 (C-O stretch.), 874 (loop for di substitution at phenyl ring), 696 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm): 9.15 (s, 1H benzthiazole ring proton at C_8), 8.38-8.36 (d, 2H phenyl ring protons at C_3 & C_5), 8.32-8.30 (d, 1H benzthiazole ring proton at C_6), 8.26-8.24 (d, 1H benzthiazole ring proton at C_5), 8.23-8.21 (d, 2H phenyl ring protons at C_2 & C_6), 4.55 (s, 2H, -SC<u>H</u>$_2$- at oxadiazole ring); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.8 (C_2 carbon at benzthiazole ring), 164.6 (oxadiazole ring carbon at phenyl linkage), 163.6(oxadiazole ring carbon at thiomethyl linkage), 154.7 (C_9 carbon at benzthiazole ring), 146.6 (C_7 carbon at benzthiazole ring), 147.8 (C_4 carbon at phenyl ring), 141.5 (C_4 carbon at benzthiazole ring), 132.5 (C_1 carbon at phenyl ring), 130.7 (C_2 & C_6 carbons at phenyl ring), 128.6 (C_3 & C_5 carbons at phenyl ring), 122.7 (C_5 carbon at benzthiazole ring), 119.6 (C_6 carbon at benzthiazole ring), 117.8 (C_8 carbon at benzthiazole ring), 34.5 (-S<u>C</u>H$_2$- carbon at oxadiazole ring); m/e (ESI): 415 (M^+).

(L) 2-(4-methoxyphenyl)-5-(((5-nitrobenzo[d] thia zol-2-yl)thio)methyl)-1,3,4-oxadiazole [compound 6l]: Yield: 60.9 %; M.P. 220- 225 ^{0}C; Anal. Cal. for $C_{17}H_{12}N_4O_4S_2$: C, 50.99; H, 3.02; N, 13.99; O, 15.98; S, 16.02 %; found: C, 50.97; H, 3.03; N, 13.97; O, 16.00; S, 16.03%; FT-IR (νmax): 3058 (Aromatic C-H strech.), 2963 (Asym. aliphatic C-H strech.), 2859 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1617 (C=N stretch.), 1601 (Phenyl ring stretch.), 1549 (Asym. N=O stretch.), 1512 (Phenyl C-H out of plane bending), 1466 (CH_2 bending), 1459 (Asym CH_3 bending), 1388 (Sym. CH_3 bending), 1357 (Sym. N=O stretch.), 1278 (C-N Strech), 1247 (methoxy Asym. C-O strech), 1156 (oxadiazole ring C-O stretch.), 1037 (methoxy sym. C-O strech), 876 (loop for di substitution at phenyl ring), 698 (C-S stretch) cm^{-1}; ^{1}H-NMR ($CDCl_3$) (δ, ppm) 9.17 (s, 1H benzthiazole ring proton at C_8), 8.32-8.30 (d, 1H benzthiazole ring proton at C_6), 8.25-8.22 (d, 1H benzthiazole ring proton at C_5), 8.01-8.00 (d, 2H phenyl ring protons at C_2 & C_6), 7.03-7.01 (d, 2H phenyl ring protons at C_3 & C_5), 4.55 (s, 2H, -SC<u>H</u>$_2$- at oxadiazole ring), 3.84 (s, 3H, Ph-OC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) (δ, ppm): 164.4 (C_2 carbon at benzthiazole ring), 164.1 (oxadiazole ring carbon at phenyl linkage), 163.5(oxadiazole ring carbon at thiomethyl linkage), 160.3 (C_4 carbon at phenyl ring), 154.6 (C_9 carbon at benzthiazole ring), 146.7 (C_7 carbon at benzthiazole ring), 141.4 (C_4 carbon at benzthiazole ring), 122.7 (C_5 carbon at benzthiazole ring), 119.6 (C_6 carbon at benzthiazole ring), 118.7 (C_1 carbon at phenyl ring), 117.5 (C_8 carbon at benzthiazole ring), 115.5 (C_2 & C_6 carbons at phenyl ring), 114.6 (C_3 & C_5 carbons at phenyl ring), 55.6 (methoxy carbons at phenyl ring), 34.6 (-S<u>C</u>H$_2$- carbon at oxadiazole ring); m/e (ESI): 400 (M^+).

Evaluation of anti-diabetic activity in alloxan-induced diabetic rats

The LD50 values of the synthesized compounds were estimated to be in the range of 300-2000 mg/kg b.w. Alloxan induces diabetes through rapid depletion of β-cells which ultimately results to reduce the insulin release. The antidiabetic activity of synthesized compounds 6(a-l) on diabetic rats were reported in Table 3.

Table 3:Antidiabetic activity of synthesized compounds 6(a-l) on diabetic rats

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in B.G.
		0th day	7th day	14th day	21st day	
1.	**Normal Control**	105.09± 1.2	102±0.3	102±0.9	100±1.2	-
2.	**Diabetic Positive control**	274±1.3	273±1.6	271±1.4	270±1.9	-
3.	**Glibenclamide 10 mg/kg**	311±2.1	239±2.4	178±1.8	103±1.7	66.88 %
	Each Test Group receives 350 mg/kg (p.o.) as effective dose.					
4.	6a	288±3.4	263±2.2	195±0.5	186±3.2	35.40%
5.	6b	305±1.4	272±2.8	226±1.3	178±2.3	41.63%
6.	6c	272±1.7	273±3.2	199±1.6	170±2.9	37.05%
7.	6d	270±1.9	259±2.7	208±1.9	179±1.5	33.70%
8.	**6e**	**366±4.2**	**255±2.7**	**205±1.5**	**135±2.6**	**63.11%**
9.	**6f**	**365±3.6**	**334±3.4**	**208±2.2**	**121±1.8**	**66.84%**
10.	**6g**	**398±1.3**	**262±2.5**	**204±1.4**	**140±3.1**	**64.82%**

11.	**6h**	**303±1.5**	**259±2.5**	**198±1.1**	**129±1.8**	**57.42%**
12.	6i	298±2.7	253±3.1	202±0.8	154±3.3	48.32%
13.	**6j**	**307±1.6**	**254±2.6**	**199±2.2**	**142±2.4**	**53.74%**
14.	6k	317±2.8	286±2.3	227±1.9	159±2.1	49.84%
15.	6l	299±2.8	255±2.9	202±1.3	162±4.1	46.91%

Discussion

All the synthesized derivatives were also confirmed by FTIR, ^{1}H NMR, C^{13}NMR and mass spectroscopy method. The FTIR spectrums were shown the significant peaks at 3060-3045 (Aromatic C-H strech.), 2970-2960 (Asym. aliphatic C-H strech.), 2865-2855 (Sym. aliphatic C-H strech.), 1665- 2000 (overtone for substitution on aromatic ring), 1610-1620 (C=N stretch.), 1605-1595 (Phenyl ring stretch.), 1520-1505 (Phenyl C-H out of plane bending), 1470-1465 (CH_2 bending), 1460-1455 (Asym CH_3 bending), 1395-1385 (Sym. CH_3 bending), 1280-1270 (C-N Strech), 1160-1150 (C-O stretch.), 880-870 (loop for di substitution at phenyl ring), 695-685 (C-S stretch) cm^{-1}. The different substitutions on phenyl ring were confirmed through FTIR spectrum peaks at 3450-3350 cm^{-1} (N-H stretch.) for amino group, 1250 (Asym. C-O strech.) & 1040 (Sym. C-O stretch.) for methoxy group, 1550 (Asym. N=O stretch.) & 1350 (Sym. N=O streching) for nitro group substitution. The proton NMR spectrums were also confirmed the different substitutions on phenyl as well as benzothiazole ring through significant signals due to change in environment of protons. Similarly the environment surrounding carbon atoms were also changed through different substitutions which were confirmed through the C^{13}NMR. The mass spectroscopy studies were confirmed the molecular weight of derivatives through molecular ion peak on mass spectrum (i.e. peak at highest m/e). . All the results of antidiabetic activity of synthesized compounds 6(a-l) on diabetic rats summarized in Table 3 revealed that most of the synthesized compounds exhibited antidiabetic response at the end of twenty first day of experimental period. It has been found that oral administration of synthesized compounds 6e, 6f, 6g, 6h and 6j caused a more significant reduction in blood glucose than other compounds in diabetic rats. However, the compound 6f at 350 mg/kg b.w. exerted maximum glucose lowering effects whereas 6d showed minimum glucose lowering effects. The maximum glucose lowering effects of compound 6i may be due to the presence of heterocyclic amine (morpholine).

Conclusion

All the newly oxadiazole containing benzothiazole derivatives were synthesized by sequencing scheme and confirmed by different spectroscopy methods. The physicochemical properties were characterized and evaluated their anti diabetic activity for all synthesized derivatives in alloxan induced diabetic rat model. Amongst all these synthesized derivatives compound 6g shown more potent anti diabetic activity at 350 mg/kg p.o.

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Abbreviations

Mol. Wt.	:	Molecular Weight
M.P.	:	Melting Point
Stretch	:	Strechning
Sym	:	Symmetric
Asym	:	Asymmetric
BG	:	Blood Glucose

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