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DESIGN, SYNTHESIS, CHARACTERIZATION AND EVALUATION OF BENZOXAZOLE DERIVATIVES FOR THEIR ANTIHYPERGLYCAEMIC ACTIVITY

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ABSTRACT

A series of analogue and derivatives of heterocyclic bearing nitrogen, oxygen, sulphur and oxazole moiety constitutes the core structure of a several biological active compounds. Benzoxazole nucleus containing heterocyclic compounds plays an important role in medicinal chemistry and exhibit wide range of biological activities such as antihyperglycaemic, antidepressant, antibacterial, antifungal, antiinflammatory, antispasmodic, antiallergic and antiasthemetic activity. The present study describes the design, synthesis and in vivo testing of new series of benzoxazole derivatives (S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-phenylphenylsulfonamido)ethanethioate)) as antihyperglycaemic agents in alloxan induced diabetic Wistar albino rats. Pioglitazone used as a standard drug. Most of the compounds showed significant antihyperglycaemic activity when compared with the standard drug pioglitazone. The structures of all synthesized compounds were determined by their IR, 1H NMR and MASS spectral analysis.

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Introduction

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar or glucose) or when the body cannot effectively use the insulin [1-5]. Diabetes mellitus has now assumed epidemic proportions in many countries of the world. With the present population of 19.4 million diabetics, and approximately 60 million by the year 2025, India would rank first in its share of the global burden of diabetes [6]. Diabetes mellitus is characterized by derangement in carbohydrate, protein, and fat metabolism caused by complete or relative insufficiency of insulin secretion and/or insulin action [7,8]. Developing countries such as India have had the maximum increases in the last few years. The current prevalence of type 2 diabetes is 2.4% in the rural population and 11.6% in the urban population of India. It has been estimated that by the year 2025, India will have the largest number of diabetic subjects in the world [9]. Diabetes mellitus is a heterogenous group of disorders characterized by high blood glucose levels [10].

A series of analogue and derivatives of heterocyclic bearing nitrogen, oxygen, sulphur and oxazole moieties constitutes the core structure of a several biological active compounds [11,12]. Benzoxazole containing 2,4-thiazolidinedione heterocyclic compounds plays an important role in medicinal chemistry and exhibit wide range of biological activities [13-17] Thiazolidinediones (TZDs)/glitazones class of insulin sensitizers have been used widely for management of type 2 diabetes mellitus. Clinical agents which were prescribed from this class are pioglitazone, rosiglitazone, troglitazone and ciglitazone [18] Ciglitazone was withdrawn because of its severe side effects irrespective of its potential insulin sensitizer property. However, the thiazolidinedione which has been recently withdrawn was developed and allowed to use in clinically at the time

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when not much scientific data were available on structures and transcriptions of peroxisome proliferator-activated receptors (PPARs), enzymes involved in diabetic mellitus [19]. Recent advances have helped and provided clear understanding of PPARs and therefore medicinal chemists are now keenly focusing their attention on the synthesis of newer analogues of this class by varying lipophilic cyclic tail, incorporating various five/six membered sulphur/nitrogen/oxygen heterocycles and keeping acid head of the classical TZDs system intact. In view of the biological importance of benzoxazole ring containing compounds, in the present work, it is planned to designing and synthesizing of benzoxazole derivatives having 2,4-thiazolidinedione heterocyclic ring. This was expected to give more potent antihyperglycaemic activity and minimum side effect comparatively exiting antihyperglycaemic drugs.

Pharmacophoric pattern of well established and structurally different antihyperglycaemic drugs like pioglitazone, rosiglitazone and troglitazone are having pharmacophoric sites as lipophilic tail, aromatic ethereal linkage and linkers. Work of many researchers indicated that the structure of a compound in which classical lipophilic tail of the thiazolidinediones when replaced by heterocyclic moieties like benzoxazolyl, 2-pyridyl, thiazolyl and oxazolyl then such thiazolidinediones have displayed promising antihyperglycaemic activity. The linkers (A,B and C; Glyburide) having one or more than one alkyl, phenyl or alkenyl carbon (s) as pharmacophores have also been found useful in designing thiazolidinedione for obtaining better insulin sensitizing property. Therefore, researcher are now paying more attention on designing and generating library of new 2,4-thiazolidinediones incorporating heterocyclic ring, in search of safe and more effective insulin sensitizers to manipulate and treat type 2 diabetes mellitus and its complications.

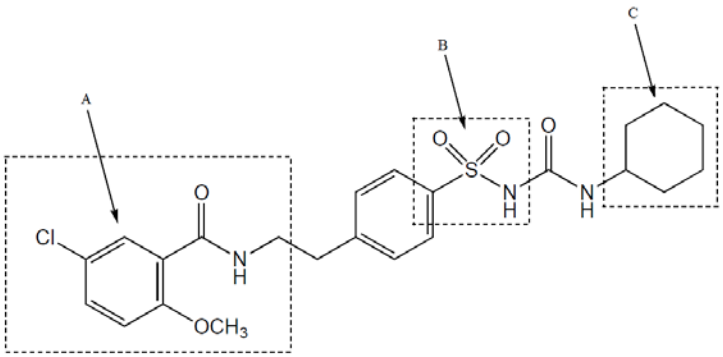
MATERIALS AND METHODS

Chemicals and Instruments

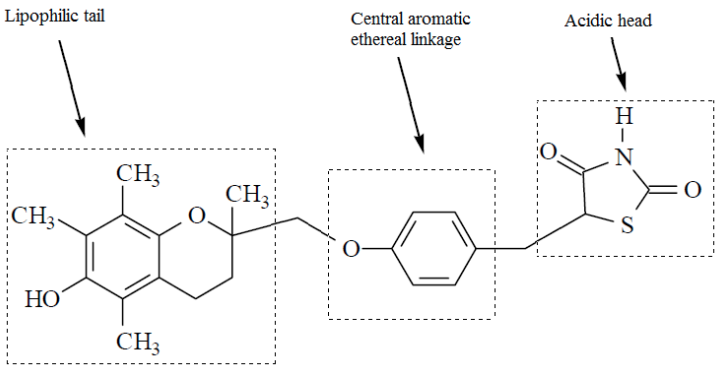
All reagents, solvents and catalyst were of LR grade and purchased from Loba Chemie Ltd., Mumbai 400 005, India. The melting point were determined in open capillary tubes and are uncorrected. The Purity of the compounds were checked on Silica gel-G coated plates were used for TLC, spots were visualized by exposure of iodine vapour in an iodine chamber. The structures of all the new synthesized compounds were confirmed by spectral analysis using IR; model Bruker alpha-T, 1H NMR; AV-II 400 and MASS; Quattro IIQ- TOF MS ES.

Designing of Benzoxazole Derivatives

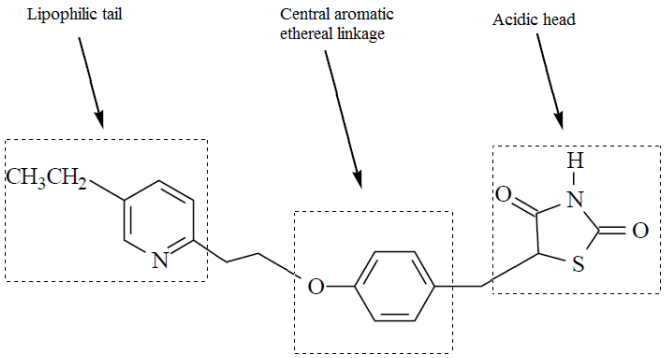
Benzoxazole derivatives are well explored as therapeutic agents because of their crucial role in various biological activity and some of them have displayed antihyperglycaemic activity.2-22 Literature revels that there is scanty information on designing and synthesizing of 2,4-thiazolidinediones having substituted benzoxazole as a lipophilic tail, 2,4-thiazolidinedione as an acidic head and no carbon chain as a linker. Considering the above facts in mind new antihyperglycaemic drugs here an attempt has been made to design and synthesize new prototypes having pharmacophores like benzoxazole, 2,4-thiazolidinediones and aromatic thioethereal alkyl group as central linker in single molecular architectural framework to achieve the new entities with better antihyperglycaemic activity.



Glyburide



Troglitazone



Pioglitazone

Figure 1: Pharmacophoric pattern of well-established antihyperglycaemic drugs

On this basis of strategy for synthesis of benzoxazole derivatives was planned in such a way that the structure of synthesized compounds possess above mentioned pharmacophoric elements.

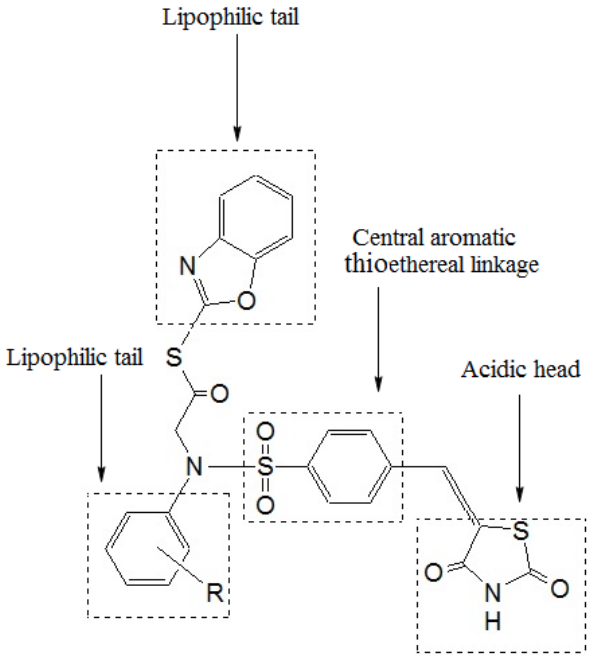


Figure 2: Designed benzoxazole derivatives

This research work deal with design & synthesize of new benzoxazole derivatives by incorporating thiazolidinedione moiety in benzoxazole framework and screen them for antihyperglycaemic activity.

Synthesis Benzoxazole Derivatives
2-Mercaptobenzoxazole (2MB):

A mixture of 37.06 gm (0.34 mole) of o-aminophenol, 19 gm (0.34 mole) of potassium hydroxide and 26 gm (21 ml, 0.34 mole) of carbon disulfide, 300 ml of 95% ethanol and 45 ml of water in a 1 liter RBF was heated under reflux for 3 hours. Norit (activated charcoal; 12gm) was added cautiously and the mixture was heated at the reflux temperature for 10 minutes. The Norit was removed by filtration. The filtrate was heated to 60-70oC, 300 ml of tap water (60-70oc) was added, then 25 ml of acetic acid in 50 ml of water was added with stirring. The product was separated as beige-white crystals and the mixture was placed in refrigerator for 3 hours to complete the crystallization. The product was collected on a buchner funnel and dried overnight at 40 0C. The product was recrystallized from 95% ethanol used as a solvent. Yield: 77.71%, m.p.: 190-193 oC, Rf : 0.84; IR (KBr): 3010, 1622-1460, 854-706 (aromatic ring), 2580 (-SH), 1581(C=N), 910 (C-O-C) cm-1; 1H (400 MHz): δ 7.60-7.12 (m, 4H, ArH), 3.48 (s, 4H, SH); MS: 151.1 m/z.

1-Chloroacetyl-2-mercaptobenz- oxazole 2MB-1:
An equimolar solution of 2-mercaptobenzoxazole 30 gm (0.2 mol) and chloroacetylchloride 15.9 ml (0.2 mol) in chloroform (100 ml) in the presence of anhydrous potassium carbonate (2gm) was refluxed on a water bath for about 5 hours. The solvent was removed under reduced pressure and the solid was purified by recrystallization from methanol. Yield 78.35%; mp 110-

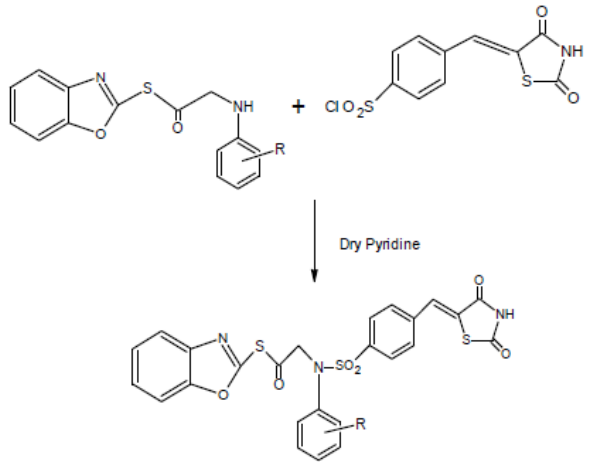
1120C; Rf : 0.65; IR (KBr): 3010, 1645-1460, 854-706 (aromatic ring), 2828 (CH2), 698 (C-S), 910 (C-O), 1617 (S-C=O), 745 (C-Cl); 1H NMR (400 MHz): δ 7.60-7.18 (m, 4H, Ar-H), 4.49 (s, 2H,-CH2); MS: 227.6 m/z.

5-Benzylidene-2,4-thiazolidinedione (TZD-1):
In a 250 ml three necked round-bottomed flask, benzaldehydes (20 gm, 0.188 mol) and 2,4-thiazolidinedione (22 gm, 0.188 mol) were together suspended in ethanol. A catalytic amount of piperidine (1ml) was added. The mixture was stirred and refluxed. After the complete removal of water and when the temperature reached above 110 °C the reaction mixture was stirred for a further 1 hr. On cooling, the product precipitated out from ethanol. The compound was filtered and washed with cold dry toluene and dry ethanol. Yield 92.89%; mp 240-2420C; Rf : 0.61; IR (KBr): 3020, 1628-1463, 804-700 (aromatic ring), 646 (C-S-C), 1747 (C-O-C), 3443 (-NH), 3034 (=CH); 1H NMR (400 MHz): δ 7.55-7.26 (m, 5H, Ar-H), 9.91 (s, 1H, -NH), 8.2 (s, 1H, =CH); MS: 205.9 m/z.

4'-Chlorosulphobenzylidine-2,4-thiazolidinedione (TZD-2):
Compound TZD-1 (8 gm, 0.0388 mol) was placed in a 100 ml round-bottomed flask equipped with a condenser and a dropping-funnel. Chlorosulphonic acid (18.08 gm, 0.155 mol) was added at room temperature using the dropping funnel. The reaction was found to be exothermic. After addition of chlorosulphonic acid was over, the reaction mass was refluxed for 1 hr on a water bath. The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a one litre beaker. The product was filtered and dried. The product was purified by recrystallization from ethanol. Yield 66.61%; mp 181-1820C; Rf : 0.69; IR (KBr): 3020, 1628-1463, 804-700 (aromatic ring), 646 (C-S-C), 1747 (C-O-C), 3443 (-NH), 3034 (=CH), 1377(S-Cl), 1547(S=O); 1H NMR (400 MHz): δ 7.59-7.26 (m, 2H, Ar-H), 7.62-7.60(dd, 2H, Ar-H), 9.94 (s, 1H, -NH), 8.25 (s, 1H, =CH); MS: 303.7 m/z.

S-1,3-benzoxazol-2-yl (phenylamino) ethanethioate (2MB-2-1):
In a 500 ml RBF fitted with reflux condenser, a mixture of 1-chloroacetyl-2-mercaptobenzoxazole (2.27 gm, 0.01 mol) and aniline (0.93 ml, 0.01 mol) in presence of anhydrous potassium carbonate used methanol (50 ml) as solvent was refluxed on a water bath for about 5 hours. After cooling, the solvent was removed under reduced pressure and the residue was dried. The resulting solid was recrystallized from mixture of chloroform: methanol (1:2). Yield 72.08%.; mp 117-118 0C; Rf: 0. 0.64; IR (KBr): 3010, 1622-1460, 854- 706 (aromatic ring), 2828 (CH2), 690 (C-S-C), 910 (C-O-C), 1581 (C=N), 1617(S-C=O), 3352 (-NH); 1H NMR (400 MHz): δ 7.60-7.43 (m, 5H, Ar-H), 7.21-6.90 (m, 4H, Ar-H), 4.20(s, 2H, CH2), 4.08 (s, 1H, -NH); MS: 284.3 m/z.
Other compounds of this series (2MB-2-2 to 2MB-2-23) were prepared in the similar way using compound (2MB-1) and various substituted aromatic amine. Physical data of compounds (2MB-2-2 to 2MB-2-23) aregiven in Table I.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-phenylphenylsulfonamido)ethanethioate (BD-1)
In a 100 ml RBF fitted with reflux condenser, a mixture of S-1,3-benzoxazol-2-yl (phenylamino)ethanethioate (2MB-2-1) (1.42 gm, 0.005 mol) and 5-(4-Chlorosulfonylbenzylidene)-2, 4- thiazolidenedione (TZD-2) (1.52 gm, 0.005 mol) and ethanol (50 ml) used as solvent. To this catalytic amount of dry pyridine (0.2 ml) was added. The mixture was refluxed with stirring on a water bath for about 7 hours. After the completion of reaction, ice-cold water was added to the reaction mixture and precipitated solid was separated by filtration and the residue was dried. The resulting solid was recrystallized from ethanol. Other compounds of this series (BD-2 to BD-23) were prepared in the similar way using compound 5-(4-Chlorosulfonylbenzylidene)-2, 4-thiazolidenedione (TZD-2) and compound (2MB-2-2 to 2MB-2-23) respectively. Physical data of compounds (BD-1 to BD-23) are given in Table I.



Scheme

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-phenylphenylsulfonamido)ethanethioate (BD-1):
IR (KBr): 3033, 1622-1475, 910-721 (aromatic ring), 2958 (C-CH2), 705 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3382 (NH), 1180-1160 (N-SO2) 1743-1717(C=O), 3020 (=C-H); 1H

NMR (400 MHz): δ 7.58-7.51 (m, 4H, Ar-H), 7.35-7.26 (m, 5H, Ar-H), 7.88-7.86 (dd, 2H, Ar-H), 7.58- 7.56 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.39 (s, 2H, CH2), 9.96 (s, 1H, NH); MS: 551.6 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-o-tolylphenylsulfonamido)ethane- thioate (BD-2):

IR (KBr): 3030, 1622-1475, 910-720 (aromatic ring), 2833,2275,2245 (C-CH2), 703 (C-S-C), 1128-985 (C-O-C), 1609-1410 (C=N), 1685 (S-C=O), 3382 (NH), 1180-1160 (N-SO2) 1743-1717 (C=O), 3028 (=C-H) 1370 (CH3); 1H NMR (400 MHz): δ 7.88-7.86 (dd, 2H, Ar-H), 7.58-7.56 (dd, 5H, Ar-H), 7.54-7.51 (m, 4H, Ar-H), 7.35-7.31 (m, 5H, Ar-H), 6.87-6.84 (m, 4H, Ar-H),7.60 (s, 1H, =CH), 4.42 (s, 2H, CH2), 9.91 (s, 1H, NH) 2.35 (s, 3H, CH3); MS: 565.6 m/z.

S-benzo[d]oxazol-2-yl2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-m-tolylphenylsulfonamido)ethane- thioate (BD-3):

IR (KBr): 3030, 1622-1475, 910-721 (aromatic ring), 2830,2270,2243 (C-CH2), 708 (C-S-C), 1129-980 (C-O-C), 1609-1415 (C=N), 1690 (S-C=O), 3382 (NH), 1180-1162 (N-SO2) 1743-1725 (C=O), 3023 (=C-H) 1372 (CH3); 1H NMR (400 MHz): δ 7.54-7.51 (m, 4H, Ar-H), 7.67 (s, 1H, Ar-H), 6.87-6.84 (m, 1H, Ar-H), 6.24-6.22 (d, 1H, Ar-H), 6.20-6.18 (d, 1H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.21 (s, 2H, CH2), 9.91 (s, 1H, NH) 2.356 (s, 3H, CH3); MS: 565.6 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-p-tolylphenylsulfonamido)ethane- thioate (BD-4):
IR (KBr): 3022, 1625-1470, 910-723 (aromatic ring), 2835,2272,2245 (C-CH2), 702 (C-S-C), 1128-980 (C-O-C), 1600-1415 (C=N), 1692 (S-C=O), 3382 (NH), 1182-1160 (N-SO2) 1740-1722 (C=O), 3030 (=C-H) 1374 (CH3); 1H NMR (400 MHz): δ 7.54-7.31 (m, 4H, Ar-H), 6.84-6.82 (dd, 2H, Ar-H), 6.31-6.30 (dd, 2H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.28 (s, 2H, CH2), 9.91 (s, 1H, NH) 2.35 (s, 3H, CH3); MS: 565.6 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(2,6-dimethylphenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl-sulfonamido) ethanethioate (BD-5):
IR (KBr): 3022, 1625-1470, 910-723 (aromatic ring), 2835,2272,2245 (C-CH2), 702 (C-S-C), 1128-980 (C-O-C), 1600-1415 (C=N), 1692 (S-C=O), 3375 (NH), 1182-1160 (N-SO2) 1743-1723 (C=O), 3032 (=C-H) 1374 (CH3), 770 (CH3 m-disubstitution); 1H NMR (400 MHz): δ 7.54-7.31 (m, 4H, Ar-H), 6.87-6.84 (m, 3H, Ar-H), 7.88-7.86 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.71 (s, 1H, =CH), 4.40 (s, 2H, CH2), 9.94 (s, 1H, NH) 2.44 (s, 6H, CH3); MS: 579.6 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(2-methoxyphenyl)phenyl- sulfonamido) ethanethioate (BD-6):
IR (KBr): 3020, 1620-1460, 911-722 (aromatic ring), 2929,2273,2248 (C-CH2), 705 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3382 (NH), 1182-1160 (N-SO2) 1743-1722 (C=O), 3033 (=C-H) 1247 (OCH3); 1H NMR (400 MHz): δ 7.54-7.31 (m, 4H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 7.88-7.86 (dd, 2H, Ar-H), 6.24-6.22 (d, 1H, Ar-H), 6.84-6.82 (d, 1H, Ar-H), 7.57 (s, 1H, =CH), 4.19 (s, 2H, CH2), 9.91 (s, 1H, NH) 3.73 (s, 3H, OCH3); MS: 581.3 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(3-methoxyphenyl)phenyl-sulfonamido) ethanethioate (BD-7):

IR (KBr): 3024, 1620-1460, 911-722 (aromatic ring), 2925,2833,2273,2244 (C-CH2), 706 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3382 (NH), 1182-1160 (N-SO2) 1740-1720 (C=O), 3030 (=C-H) 1247 (Ar-OCH3); 1H NMR (400 MHz): δ 7.54-7.31 (m, 4H, Ar-H), 6.88-6.84 (m, 1H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.0 (d, 1H, Ar-H), 5.59-5.97 (d, 1H, Ar-H), 5.58 (s, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.26 (s, 2H, CH2), 9.91 (s, 1H, NH) 3.75 (s, 3H, OCH3); MS: 581.3 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(4-methoxyphenyl)phenyl-sulfonamido)ethanethioate (BD-8):
IR (KBr): 3023, 1620-1460, 911-722 (aromatic ring), 2830,2273,2244 (C-CH2), 708 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3382 (-NH), 1182-1160 (N-SO2) 1740-1720 (C=O), 3034 (=C-H) 1249 (Ar-OCH3); 1H NMR (400 MHz): δ 7.54-7.31 (m, 4H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.84-6.82 (dd, 2H, Ar-H), 6.31-6.30 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.27 (s, 2H, CH2), 9.93 (s, 1H, NH) 3.66 (s, 3H, OCH3); MS: 581.3 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(2,5-dimethoxyphenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl-sulfonamido)ethanethioate(BD-9):
IR (KBr): 3023, 1620-1460, 911-722 (aromatic ring), 2989,2833,2278,2244 (C-CH2), 705 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3382 (NH), 1182-1160 (N-SO2) 1740-1720 (C=O), 3030 (=C-H) 1247 (Ar-OCH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.44-6.42 (d, 1H, Ar-H), 5.99-5.97 (d, 1H, Ar-H), 5.83 (s, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.27 (s, 2H, CH2), 9.90 (s, 1H, NH) 3.79 (s, 6H, OCH3); MS: 611.4 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(2-ethylphenyl)phenyl-sulfonamido)ethanethioate (BD-10):

IR (KBr): 3010, 1640-1460, 911-722 (aromatic ring), 2833,2273,2244 (C-CH2), 709 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1690 (S-C=O), 3300 (NH), 1182-1160 (N-SO2) 1760-1720 (C=O), 2990 (=C-H) 1300,800 (CH2-CH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.87-6.84 (m, 1H, Ar-H), 6.38-6.36 (d, 1H, Ar-H), 5.99-5.97 (d, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.39 (s, 2H, CH2), 9.96 (s, 1H, NH) 2.60-2.57 (q, 2H, CH2), 1.21-1.18 (t, 3H, CH2); MS: 579.9 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(3-ethylphenyl)phenyl-sulfonamido)ethanethioate(BD-11):
IR (KBr): 3010, 1620-1460, 911-722 (aromatic ring), 2830,2273,2244 (C-CH2), 705 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3300 (NH), 1182-1160 (N-SO2) 1780-1724 (C=O), 2989 (=C-H) 1300,800 (CH2-CH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.60-7.51 (m, 4H, Ar-H), 6.87-6.84 (m, 1H, Ar-H), 6.38 (s, 1H, Ar-H), 6.26-6.24 (d, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.41 (s, 2H, CH2), 9.95 (s, 1H, NH) 2.60-2.57 (q, 2H, CH2), 1.21-1.18 (t, 3H, CH2); MS: 579.9 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(4-ethylphenyl)phenyl-sulfonamido)ethanethioate (BD-12):
IR (KBr): 3017, 1620-1460, 911-722 (aromatic ring), 2838,2278,2244 (C-CH2), 705 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3378 (NH), 1182-1160 (N-SO2) 1740-1720 (C=O), 2922 (=C-H) 1300,800 (CH2-CH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.90-6.88 (dd, 2H, Ar-H), 5.34-5.32 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.29 (s, 2H, CH2), 9.91 (s, 1H, NH) 2.60-2.57 (q, 2H, CH2), 1.21-1.18 (t, 3H, CH2); MS: 579.9 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(2,6-diethylphenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl sulfonamido)ethanethioate (BD-13):
IR (KBr): 3017, 1620-1460, 911-722 (aromatic ring), 2873,2838,2278 (C-CH2), 705 (C-S-C), 1140-980 (C-O-C), 1600-1418 (C=N), 1692 (S-C=O), 3378 (NH), 1182-1160 (N-SO2) 1783-1720 (C=O), 2922 (=C-H) 1300,1247,920,855 (CH2-CH3) 770-695 (CH2-CH3 m-disubstitution); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.90-6.88 (dd, 2H, Ar-H), 6.20-6.17 (m, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.32 (s, 2H, CH2), 9.88 (s, 1H, NH); MS: 607.3 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(2-ethoxyphenyl)phenyl sulfonamido)ethanethioate (BD-14):
IR (KBr): 3010, 1622-1475, 910-721 (aromatic ring), 2960 (C-CH2), 709 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3378 (NH), 1180-1160 (N-SO2) 1748-1719 (C=O), 2980 (=C-H) 1271 (OCH2-CH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 6.24-6.22 (d, 1H, Ar-H), 3.55-3.50 (q, 2H, CH2), 1.42-1.39 (t, 3H, CH3), 7.60 (s, 1H, =CH), 4.30 (s, 2H, CH2), 9.90 (s, 1H, NH); MS: 595.5 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(3-ethoxyphenyl)phenyl-sulfonamido)ethanethioate (BD-15):
IR (KBr): 3010, 1622-1475, 910-721 (aromatic ring), 2958 (C-CH2), 705 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1688 (S-C=O), 3398 (NH), 1180-1160 (N-SO2) 1748-1717 (C=O), 2990 (=C-H) 1271 (OCH2-CH3); 1H NMR (400 MHz): δ7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.87-6.84 (m, 1H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.24-6.22 (d, 1H, Ar-H), 6.20-6.18 (d, 1H, Ar-H), 5.81 (s, 1H, Ar-H), 3.63-3.61 (q, 2H, CH2), 1.31-1.30 (t, 3H, CH3), 7.60 (s, 1H, =CH), 4.24 (s, 2H, CH2), 9.92 (s, 1H, NH); MS: 595.5 m/z.

S-benzo[d]oxazol-2-yl2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(4-ethoxyphenyl)phenyl-sulfonamido)ethanethioate (BD-16):
IR (KBr): 3010, 1622-1475, 910-721 (aromatic ring), 2958 (C-CH2), 708 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3398 (NH), 1180-1160 (N-SO2) 1743-1717 (C=O), 2990 (=C-H) 1270 (OCH2-CH3); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.90-6.88 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.34-6.32 (d, 2H, Ar-H), 3.60-3.57 (q, 2H, CH2), 1.21-1.18 (t, 2H, CH3), 7.60 (s, 1H, =CH), 4.30 (s, 2H, CH2), 9.91 (s, 1H, NH); MS: 595.5 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(2,5-diethoxyphenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl sulfonamido)ethanethioate (BD-17):
IR (KBr): 3010, 1622-1475, 910-721 (aromatic ring), 2958 (C-CH2), 705 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3398 (NH), 1180-1160 (N-SO2) 1748-1717 (C=O), 3020 (=C-H) 1270 (OCH2-CH3); 1H NMR (400 MHz): δ 7.88-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.90-6.88 (d, 1H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 5.82(s, 1H, Ar-H), 5.34-5.32 (d, 1H, Ar-H), 3.60-3.51 (qq, 4H, CH2), 1.64-1.62 (tt, 6H, CH3), 7.60 (s, 1H, =CH), 4.38 (s, 2H, CH2), 9.92 (s, 1H, NH); MS: 639.7 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(2-nitrophenyl)phenyl-sulfonamido)ethanethioate (BD-18):
IR (KBr): 3010, 1625-1478, 910-721 (aromatic ring), 2958 (C-CH2), 705 (C-S-C), 1128-985 (C-O-C), 1608-1410 (C=N), 1689 (S-C=O), 3381 (NH), 1181-1168 (N-SO2) 1748-1723 (C=O), 2980 (=C-H), 1585-1523,1373-1312 (NO2); 1H NMR (400 MHz): δ 7.96-7.94(d, 1H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.43-6.42 (d, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.26 (s, 2H, CH2), 9.95 (s, 1H, -NH); MS: 596.7 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(3-nitrophenyl)phenyl-sulfonamido)ethanethioate (BD-19):
IR (KBr): 3010, 1622-1477, 910-721 (aromatic ring), 2960 (C-CH2), 708 (C-S-C), 1130-986 (C-O-C), 1608-1410 (C=N), 1690 (S-C=O), 3392 (NH), 1180-1160 (N-SO2) 1748-1717 (C=O), 2998 (=C-H), 1589-1523,1372-1314 (NO2); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.29-7.27 (d, 1H, Ar-H), 7.54-7.33 (m, 4H, Ar-H), 7.08 (s, 1H, Ar-H), 6.95-6.94 (d, 1H, Ar-H), 6.31-6.29 (m, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.23 (s, 2H, CH2), 9.95 (s, 1H, NH); MS: 596.7 m/z.

S-benzo[d]oxazol-2-yl-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(4-nitrophenyl)phenylsulfonamido) ethanethioate (BD-20):
IR (KBr): 3010, 1622-1475, 910-721 (aromatic ring), 2958 (C-CH2), 705 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3382 (NH), 1180-1160 (N-SO2) 1748-1717 (C=O), 2990 (=C-H), 1589-1523,1371-1318 (NO2); 1H NMR (400 MHz): δ 7.99-7.97 (dd, 2H, Ar-H), 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.90-6.88 (dd, 2H, Ar-H), 7.60 (s, 1H, =CH), 4.30 (s, 2H, CH2), 9.91 (s, 1H, NH); MS: 596.0 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(2-chlorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl- sulfonamido) ethanethioate(BD-21):
IR (KBr): 3010, 1623-1472, 913-721 (aromatic ring), 2959 (C-CH2), 708 (C-S-C), 1129-988 (C-O-C), 1610-1408 (C=N), 1689 (S-C=O), 3392 (NH), 1188-1163 (N-SO2) 1748-1717 (C=O), 2993 (=C-H), 818-710 (Cl); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 7.12-7.10 (d, 1H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 6.24-6.22 (d, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.22 (s, 2H, CH2), 9.91 (s, 1H, NH); MS: 586.7 m/z.

S-benzo[d]oxazol-2-yl-2-(N-(3-chlorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl-sulfonamido)ethanethioate (BD-22):
IR (KBr): 3010, 1622-1472, 910-721 (aromatic ring), 2958 (C-CH2), 708 (C-S-C), 1128-985 (C-O-C), 1608-1407 (C=N), 1687 (S-C=O), 3398 (NH), 1180-1160 (N-SO2) 1748-1717 (C=O), 2999 (=C-H), 813-709 (Cl); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.87-6.84 (m, 1H, Ar-H), 6.62-6.61 (d, 1H, Ar-H), 6.08(s, 1H, Ar-H), 5.78-5.76 (d, 1H, Ar-H), 7.60 (s, 1H, =CH), 4.30 (s, 2H, CH2), 9.90 (s, 1H, NH); MS: 586.7 m/z.

S-benzo[d]oxazol-2-yl 2-(N-(4-chlorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl- sulfonamido) ethanethioate (BD-23):
IR (KBr): 3010, 1623-143, 910-721 (aromatic ring), 2962 (C-CH2), 709 (C-S-C), 1129-987 (C-O-C), 1609-1408 (C=N), 1689 (S-C=O), 3393 (NH), 1182-1162 (N-SO2) 1748-1719 (C=O), 2998 (=C-H), 819-712 (Cl); 1H NMR (400 MHz): δ 7.80-7.78 (dd, 2H, Ar-H), 7.58-7.56 (dd, 2H, Ar-H), 7.54-7.31 (m, 4H, Ar-H), 6.90-6.88 (m, 1H, Ar-H),7.60 (s, 1H, =CH), 4.30 (s, 2H, CH2), 9.91 (s, 1H, NH); MS: 586.7 m/z.

BIOLOGICAL SCREENING OF SYNTHESIZED COMPOUNDS23-27

Toxicity Study

Acute toxicity study was carried out as per the procedure given in OECD Guideline No. 420. The study was conducted as follows:
Experimental animals and approval of study
Healthy young adult females nulliparous and non-pregnant Wistar albino rats (150 to 300 g) were selected for the study. The animals were randomly selected and kept in their cages for at least 5 days prior to the start of dosing, to allow for acclimatisation to the laboratory conditions.
All the experimental study was conducted as per the Regulations of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The protocol of the experimental study on animals was reviewed and approved by the Local Institutional Animal Ethics Committee (Approval number 01/IAEC/2013).

Preparation of doses

The synthetic compounds were administered in a constant volume (not to be exceeding 2 mL/100g body weight of rats) over the range of doses to be tested by varying the concentration of the dosing preparation. Doses were prepared shortly prior to administration.

Administration of doses

The synthetic compounds were administered in a single dose by gastric gavage using a oral feeding needles and rats were fasted prior to dosing (e.g. with the rat, food but not water should be withheld over-night).
Selection of doses
The starting dose for the toxicity study were selected from the fixed dose levels of 5, 50, 300 and 2000 mg/kg as a dose expected to produce evident toxicity based, on evidence from in vivo and in vitro data from the same chemical and structurally related chemicals. A period of at least 24 hours were allowed between the dosing of each animal. All animals were observed for 14 days.

Numbers of animals and dose levels

A total of five rats of one sex were used for each dose level. The one rat from each group was selected for sighting study and remaining rats were used for main toxicity study as per OECD guideline.
The time interval between dosing at each level was determined by the onset, duration, and severity of toxic signs. Treatment of animals at the next dose were delayed until one was confident of survival of the previously dosed animals.

Sign and symptoms of toxicity
Rats were observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours, and daily thereafter, for a total of 14 days. The toxic reactions, time of onset and length of recovery period was determined in each rat. Changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behaviour pattern with tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma were observed in each rat. All test animals (including those that die during the test) were subjected to gross necropsy at the end of the study.

Effect of acute toxicity study of benzoxazole derivatives in rats
Results of acute toxicity study of different synthetic compounds of benzoxazole derivatives showed no sign of toxicity with doses of 5, 50, and 300 mg/kg, while 2000 mg/kg dose of different synthetic compounds of benzoxazole derivatives showed sign of toxicity and mortality. Convulsion, pilo-erection, hypo activity, shallow deep respiration, very weak heart beats and mortality were observed in animal treated with 2000 mg/kg dose of synthetic compounds. Post mortem examination revealed general congestion of all internal organs particularly the lung and heart. The heart was flabby engorged with blood, which may indicate heart failure due to edema.
According to OACD guidelines all the doses of 2000 mg/kg of different synthetic compounds of benzoxazole derivatives fall in category-5 and considered to be toxic. While 5, 50, and 300 mg/kg doses of different synthetic compounds fall in category-4 (nontoxic). Therefore the LD50 of these synthetic compounds were found to be more than 300 mg/kg body weight. It indicates that the derivatives of benzoxazole having the cut off LD50 near to 500 mg/kg as per OECD guidelines no 420.
Therapeutic range was considered between 1/20 to 1/4 times of LD50 for any synthetic compound. Accordingly, 50 mg/kg doses of different synthetic compounds of benzoxazole derivatives were selected for antihyperglycaemic activity in alloxan induced diabetic rats.

Antihyperglycaemic Activity in Alloxan Induced Diabetes rats
The synthetic compounds were evaluated for their in-vivo antihyperglycaemic activity in albino Wistar rats using alloxan induced diabetes method.

Experimental animals and approval of study
Adult male and female albino Wistar rats weighing between 150 and 300 g were used in this study. All the experimental study was conducted as per the Regulations of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The protocol of the experimental study on animals was reviewed and approved by the Local Institutional Animal Ethics Committee (Approval number 01/IAEC/2013).

Housing and feeding of animals
The animals were housed in clean polacrylic cages (38x23x10 cm) with not more than five animals per cage and they were acclimatized under standard laboratory conditions (temperature 25±2°C) and light cycle (12 h light and 12 h dark). All animals were fed with standard pellet diet and water ad libitum.

Preparation and selection of doses
The doses of synthetic compounds were taken as 50 mg/kg of body weight. The selection of doses of synthetic compounds was selected on the basis of toxicity study conducted on rats as per OECD guideline. Doses were prepared in normal saline shortly prior to administration.

Administration of doses
The synthetic compounds were administered in a single dose by gastric gavage using a oral feeding needles and rats were fasted prior to dosing (e.g. with the rat, food but not water should be withheld over-night).

Induction and assessment of diabetes
Diabetes was artificially induced by intraperitonially injection of freshly prepared solution of alloxan in 0.1 M citrate buffer that's PH was adjusted to 4.5 and temperature of the solution was maintained in between 2 to 8 0C at the dose of 110 mg/kg body weight to overnight fasted rats. The blood sample of rats were collected through snipping the tail vein. The diabetic status of rats were confirmed post 48 hr of alloxan injection by monitoring blood glucose level with the help of Glucometer. The rats which having blood glucose levels more than 200 mg/dl were considered as diabetic and selected for the study.

Experimental design
A total of 130 Healthy albino Wistar rats were marked and randomly distributed into 26 groups of 5 animals in each group. All the animals were fasted overnight. The groups were divided as follows:
Group (I):- Normal control Group (normal rats were receivied vehicle only)
Group (II):-Diabetic control Group (alloxan induced diabetic rats were receivied vehicle only)
Group (III) to (XXV):- Test Groups (Alloxan induced diabetic rats were receivied synthetic compounds BD-1 to BD-23 in a dose of 50 mg/kg).
(XXVI):- Standard Group (Alloxan induced diabetic rats were receivied Pioglitazone as a standard drug in a dose of 30 mg/kg).

Blood sampling and biochemical analysis

The blood sample of rats were collected through snipping the tail vein. Blood sample were collected at day 0, 3, 7 and 14 for all 26 groups of rats. The blood samples were collected in micro centrifuge tubes (Eppendorf tubes) and centrifuge for 10 minutes at 10,000 rpm. Blood glucose level was estimated with the help of Glucometer. The blood glucose level was expressed as mg/dl of blood.

Statistical Analysis

All the results were expressed as mean±SEM. The data obtained in the study was subjected to one way analysis of variance (ANOVA) followed by dunnett test for determining the significance. P-value <0.05 was to be considered for statistical significant.

One way analysis of variance (ANOVA) followed by dunnett test. Value are expressed as mean ± SEM; n= number of animals. P>0.05 was considered as non-significant, *P<0.05 was considered as significant. **P<0.005 was considered highly significant, ***P<0.0005 was considered as very highly significant.

RESULTS AND DISCUSSION

All the synthesized compounds of benzoxazole derivatives were screened for their antihyperglycaemic activity against alloxan induced diabetic control rats, Pioglitazone were used as a standard drug. The screening results revealed that the compounds BD-5, BD-6, BD-10, BD-12, and BD-14 exhibited highest hypoglycemic activity while compounds BD-1, BD-2, BD-4, BD-7, BD-8, BD-9, BD-11, BD-13, BD-15, BD-16, BD-17, and BD-2 exhibited moderate hypoglycemic activity. Compounds BD-3, BD-18, BD-19, BD-21 and BD-23 exhibited weak hypoglycemic activity and compounds BD-22 was not more effective to lowering blood glucose level. The results of antihyperglycaemic activity of all test compounds are depicted in table no.2.
Compounds with di-ortho substituted methyl group, methoxy group at ortho position, ethyl group at ortho position, ethoxy group at ortho position, ethyl group at para position on N,N-disubstituted aniline ring were gave maximum activity and compound with meta substitution on N,N-disubstituted aniline ring & nitro and chloro substitution at ortho, para and meta position on N,N-disubstituted aniline ring were gave minimum activity.

CONCLUSION

In the present work, benzoxazole derivatives were designed and synthesized by studying the pharmacophoric pattern of well established and structurally different antihyperglycaemic drugs and evaluated for antihyperglycaemic activity. The compounds BD-5, BD-6, BD-10, BD-12, and BD-14 exhibited highest hypoglycemic activity and compounds BD-22 was not more effective to lowering blood glucose level. It was concluded that N,N-substituted aniline ring having orhto and para substitute as methyl, ethyl methoxy and ethoxy and di-ortho substituted methyl group, these compound were showed maximum antihyperglycaemic activity in alloxan induced diabetic albino Wistar rats. This investigation thus indicates the importance of these benzoxazole derivatives as potential lead candidates.

Table 1: Percentage yield, m.p. ranges and Rf values of synthesized compounds

S.No.	Compound Code	Percentage (%) Yield	M.P. Range (^{o}C)	Rf value
1.	2MB	77.71%	190-193	0.84
2.	2MB-1	78.35%	110-112	0.65
3.	TZD-1	92.89%	240-242	0.61
4.	TZD-2	66.61%	181-182	0.69
5.	2MB-2-1	72.08%	117-118	0.64
6.	2MB-2-2	75.42%	124-126	0.61
7.	2MB-2-3	73.73%	129-130	0.76
8.	2MB-2-4	68.01%	139-140	0.81
9.	2MB-2-5	59.16%	161-163	0.72
10.	2MB-2-6	69.64%	154-155	0.78
11.	2MB-2-7	72.52%	173-175	0.68
12.	2MB-2-8	59.74%	189-190	0.66
13.	2MB-2-9	66.18%	184-185	0.71
14.	2MB-2-10	59.48%	144-145	0.56
15.	2MB-2-11	67.20%	159-160	0.50
16.	2MB-2-12	58.52%	132-133	0.60
17.	2MB-2-13	43.36%	204-205	0.54
18.	2MB-2-14	64.52%	196-197	0.75
19.	2MB-2-15	57.18%	211-212	0.70
20.	2MB-2-16	75.84%	198-200	0.57
21.	2MB-2-17	53.36%	227-228	0.87

22.	2MB-2-18	44.20%	246-248	0.67
23.	2MB-2-19	61.58%	266-267	0.73
24.	2MB-2-20	78.04%	178-179	0.69
25.	2MB-2-21	59.62%	145-147	0.55
26.	2MB-2-22	67.50%	159-161	0.51
27.	2MB-2-23	56.46%	188-189	0.53
28.	BD-1	64.72%	251-252	0.75
29.	BD-2	71.63%	210-211	0.77
30.	BD-3	78.36%	274-275	0.66
31.	BD-4	52.48%	219-221	0.64
32.	BD-5	58.13%	236-237	0.48
33.	BD-6	65.17%	206-207	0.75
34.	BD-7	77.24%	267-269	0.77
35.	BD-8	73.79%	212-214	0.67
36.	BD-9	61.96%	297-298	0.81
37.	BD-10	72.31%	233-234	0.68
38.	BD-11	65.91%	283-284	0.64
39.	BD-12	62.97%	272-273	0.73
40.	BD-13	69.63%	292-293	0.52
41.	BD-14	74.42%	295-296	0.78
42.	BD-15	71.38%	278-279	0.74
43.	BD-16	62.96%	259-260	0.65
44.	BD-17	67.08%	309-310	0.86
45.	BD-18	68.68%	241-243	0.69
46.	BD-19	75.42%	213-214	0.82
47.	BD-20	63.63%	263-264	0.74
48.	BD-21	72.28%	224-225	0.56
49.	BD-22	81.50%	307-308	0.59
50.	BD-23	57.53%	322-323	0.53

Table 2: Effect of benzoxazole derivatives on blood glucose level after daily administration for 14 days

Groups and Treatment (n=5)		**Blood glucose level (mg/dl)**			
		Day 0	**Day 3**	**Day 7**	**Day 14**
I.	Normal control	107.9±3.87	108.92±3.11	110.84±2.98	111±3.64
II.	Diabetic control	258.2±6.72	252.8±6.28	251.6±4.87	259±8.40
III.	BD-1	247.6±12.23	224.6±8.68	183.4±3.90**	133.2±2.31***
IV.	BD-2	241.8±7.57	217±4.74*	173.4±4.15***	132.2±2.24***
V.	BD-3	227.8±2.69	210.8±6.71	197.2±6.93*	140.6±4.55***
VI.	BD-4	237.6±6.37	227.8±6.55*	202.2±9.41	130.4±1.02***
VII.	BD-5	246±11.86	222.2±7.69	178.8±3.18*	127.4±2.13***
VIII.	BD-6	244.4±7.37	217±4.78	172.6±4.03**	127.4±1.50***
IX.	BD-7	233.2±3.42	213.6±7.82	185±13.10*	133±1.48***
X.	BD-8	241±3.11	225.4±4.15*	184.8±5.38***	134.6±4.43***
XI.	BD-9	247.2±6.35	221.4±8.60	185±5.02*	135.4±1.07***
XII.	BD-10	238±9.46	217.2±4.69	173.2±6.06**	126.6±1.86***
XIII.	BD-11	235.4±6.4	223.4±5.39*	187.6±9.19***	138.2±3.92***
XIV.	BD-12	237.2±3.55	225.2±3.97	190.8±8.54*	123.8±2.47***
XV.	BD-13	251.6±11.85	226±4.64	176.6±3.15*	132.6±2.13***
XVI.	BD-14	242±6.72	216.4±4.77*	161.2±2.93***	120±2.04***
XVII.	BD-15	255.4±7.21	227.6±2.85	183±8.37*	133.6±2.73***
XVIII.	BD-16	250.6±5.67	226.2±2.41	206±5.67**	135.4±2.76***
XIX.	BD-17	247.6±5.25	224.6±6.31**	184±5.10***	137.2±2.59***
XX.	BD-18	246.8±4.21	224.4±2.24	182.4±4.83*	143.4±2.37***
XXI.	BD-19	238.8±1.56	224.5±1.5	184.5±6.95**	143±2.12***
XXII.	BD-20	254.8±5.03	233±2.16*	171.8±5.84***	138.2±1.77***
XXIII.	BD-21	258.8±8.81	225.4±1.91	179.8±5.51**	145.8±2.98***
XXIV.	BD-22	246.6±9.08	228.2±5.85	188.6±6.38*	152.8±2.47***
XXV.	BD-23	236±2.73	219.4±3.86**	178.8±8.62***	140.4±2.13***
XXVI.	Standard Drug (Pioglitazone)	253±7.85	194±6.76**	126±2.19***	101.6±0.67***

One way analysis of variance (ANOVA) followed by dunnett test. Value are expressed as mean ± SEM; n= number of animals. P>0.05 was considered as non-significant, *P<0.05 was considered as significant.

**P<0.005 was considered highly significant, ***P<0.0005 was considered as very highly significant.

REFERENCES

1. Amos, A; McCarty, D and Zimmet, P (2010), "The rising global burden of diabetes and its complications: estimates and projections to the year 2010", Diabetic Med, 14, S1-S85.
2. World Health Organization (WHO) (1999), "Definition, Diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classifications of diabetes mellitus", Department of Non-communicable Disease Surveillance, Geneva,344-389.
3. Kaveeshwar, Abhijeet and Jon, Cornwall (2014), "The current state of diabetes mellitus in India", Australasian Medical Journal, 7, 1, 45-48.
4. King, H; Aubert, R and Herman, W (1998), "Global burden of diabetes, 1995-2025, Prevalence, numerical estimates and projections", Diabetes Care, 21,1414-31.
5. World Health Organization (2016), "Global Report on Diabetes", http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf, access on June 2016.
6. Page, RL; Gozansky, WS and Ruscin, JM (2003), "Possible heart failure exa cerbation associated with rosiglitazone: a case report", Pharmacother, 23, 945-954
7. Raok, et al. (2015), "Benzoxazole: the molecule of diverse pharmacological importance", International Journal of Pharmacy and Pharmaceutical Sciences, Vol 7, Issue 1, 34-56.
8. Lemberger, T,; Desvergne, B and Wahli, W (1996), "Peroxisome - proliferator-active receptors: a nuclear receptor signaling pathway in lipid physiology", Ann Rev Cell Dev Biol, 12, 335-363.
9. Miyazaki, Y et al. (2001), "Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type 2 diabetic patients", Diabetologia, 44, 2210-2219.
10. Pattan, SR; P, Kekareb; A, Patilc; A, Nikaljec and BS, Kitturd (2009), "Studies on the synthesis of novel 2,4-thiazolidinedione derivatives with antidiabetic activity", Iranian Journal of Pharmaceutical Sciences, 5(4), 225-230.
11. A.R. Deshmukha et al. (2016), "Design, Synthesis and Antidiabetic Evaluation of New Cyanoquinoloxy Benzylidenyl 2,4-Thiazolidinediones", Chemistry & Biology Interface, 6, 4, 189- 197.
12. Pattan, SR et al. (2005), "Syntheis and antidiabetic activity of 2- amino [5' (4- sulphonylbnzylidene)-2, 4-thiazolidnedione]- 7- chloro- 6- fluorobenzothiazole", Indian J Chem., Vol. 44B, 2404-2408.
13. Gopalakrishna, B; Raghunadan, N; Raov, S and Shrinivas, B (2005), "Synthesis and evaluated pharmacological activity of some new benzoxazole derivatives", Indian Drugs, 42(6), 369.
14. Joy, JM; Jacob, N and kutty, GN (2005), "Evaluation of hypoglycemic effects of 4- thiazolidindione", Indian Drugs, 42 (1), 47-51.
15. Bok, Young et al. (2003), "Synthesis and antihyperglycemic activity of erythrose, ribose and substituted pyrrolidine containing thiazolidinedione derivatives", Chem. Pharm. Bull. 51 (3) 276- 285.
16. Jeon, R and Park, S (2004), "Synthesis and biological activity of benzoxazole containing thiazolidinedione derivatives", Arch. Pharm. Res., 27, 1099-1105.
17. Arakawa, K et al. (1984), "Novel benzoxazole 2,4-thiazolidinediones as potent hypoglycemic agents. Synthesis and structure-activity relationships", Chem Pharm Bull (Tokyo), Vol.45 (12),84- 93.
18. Reddy, A et al. (2014), "Antidiabetic activity of 2-amino-(5-fluoro-2-oxoindolin-3-ylidene) benzoxazole-5-carbohydrazide in rats", Journal of Biomedical and Pharmaceutical Research", Vol. 3, Issue 6,78-81.
19. Blatt, AH (2007), Organic Synthesis Collective Volume-II, John Wiley & Sons, New York, 65-66.
20. Denis, C and Mark, V (2007), "Organic Synthesis Reaction Guide, John Wiley & sons, New York, 117-118.
21. Robjohn, N (2007), "Organic Synthesis Collective Vol. IV, John Wiley & Sons, New York, 569- 570.
22. SR, Pattana; P, Kekareb; A, Patilc; A, Nikaljec and BS, Kitturd (2009), "Synthesis of thiazolidinedione derivatives", Iranian Journal of Pharmaceutical Sciences, 5(2), 57-59.
23. (2004), "OECD (Organization for Economic Co-operation and Development) Guideline No. 420", Testing of Chemicals, Acute oral toxicity – Fixed dose Procedure.
24. H, Gerhard Vogel (2004), Drug Discovery and Evaluation, Enlarged Edition, Springer-Verlag Berlin Heidelberg, New York, 569.
25. EU, Etuk (2010), "Animals models for studying diabetes mellitus",1(2) Agriculture and Biology Journal of North America,130-134
26. EN, Carvalho et al. (2010), "Experimental Model of Induction of Diabetes Mellitus in Rats, Vol. 18, Special Edition, Available on URL: http://www.scielo.br/acb.
27. M, Sai Harika (2014), "Synergistic activity of thiadiazole and thiazolidinone derivatives against alloxan induced diabetes in rats", Sch. Acad. J. Pharm., 3(3), 301-305.