DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED SULPHONYLUREAS AND GUANIDINE DERIVATIVES AS HYPOGLYCEMIC AGENTS"

A Synopsis

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By

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CERTIFICATE

This is to certify that the synopsis entitled "**DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED SULPHONYLUREAS AND GUANIDINE DERIVATIVES AS HYPOGLYCEMIC AGENTS**" represents the work of **Mr. Ishan I Panchal** and includes the results of his own research work. Studies were carried out at the Department of Pharmaceutical chemistry, Parul Institute of Pharmacy, Vadodara under my guidance and supervision. This work is up to my satisfaction. This work embodied in this synopsis is original and no parts of the synopsis have been submitted previously to this university or any other university for the award of Ph.D. or any other degree.

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Content

1. Abstract

Diabetes mellitus is a major degenerative disease associated with a group of disorders of carbohydrate metabolism results from the body's failure to produce insulin in type 1 and insulin resistance in type 2 diabetes mellitus through altered secretion, decreased insulin activity known as hyperglycemia. There is a direct relationship between hyperglycemia and long-term complications such as, retinopathy, nephropathy and neuropathy like micro and macrovascular concerns. Search for new innocent anti-diabetic agents are still a challenge for medicinal chemists. The detailed study of literature review and study, we have decided to design and synthesis of novel antidiabetic agents with the help of the Crystal structure of the pancreatic ATP-sensitive K^+ channel SUR1/Kir6.2 complexes with ATP and glibenclamide (PDB ID: 5TWV) was imported. Docking, screening and post-analysis of the designed compounds was done using iGEMDOCK program with the protein target 5TWV. The novelty of synthesize compounds was checked by Sci Finder report. All the synthesize compounds were characterized by melting points, TLC, IR spectroscopy, Mass spectroscopy, ^{1}H-NMR and ^{13}C-NMR. The synthesized compounds were proposed for biological evaluation by most relevant animal models like alloxan (150 mg/dl, intraperitonial) induced diabetic animal model for in-vivo studies.

2. Brief description on the state of the art of the research topic

Diabetes mellitus is a major degenerative disease in the world today. It is a group of disorders of carbohydrate metabolism results from body's failure to produce insulin in Type 1 and insulin resistance in Type 2 diabetes mellitus through altered secretion, decreased insulin activity, or a combination of both factors and characterized by hyperglycaemia.[1] Several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long-term complications such as retinopathy, nephropathy, neuropathy like micro and macrovascular complications. This disease is associated with reduced life expectancy significant morbidity due to specific diabetes related micro vascular complications that diminish the quality of life. India has today become the diabetic capital of the world with over 20 million diabetics and this number is set to increase to 57 million by 2025. [2,3]

Numerous drugs such as sulfonylureas and Biguanides are presently available to reduce hyperglycaemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is essential to overcome this problems. [4] The onset of insulin in body, which causes an abnormal effect on glucose metabolism, is related not only to the development of Type II diabetes but also to cardiovascular disease. [5] Sulfonylureas are the mainstay of antidiabetic therapy for many years. Several structurally modified agents, which have been added in

Sulfonylurea class, still there is need of efficacious agents, which are sufficiently nontoxic for chronic use. [6]

The generally agreed treatment goal in T2DM is to maintain near-normal levels of glycemic control in both the fast in postprandial states. Although diet and exercise are the first steps toward achieving this goal, oral antidiabetic pharmacotherapy also plays an important role. Type 2 diabetes mellitus (T2DM) presents a major challenge to the healthcare system around the world. The current oral treatment options for T2DM include metformin, sulfonylurea or thiazolidinedione derivatives, glycosidase inhibitors and the recently Dipeptidyl Peptidase IV inhibitors which have been introduced. Antioxidants are used as supportive therapy in the treatment of DM and hypoglycemic plants have been shown to regulate the oxidative complications of DM. [7]

Sulfonylureas, the first generation of antidiabetic agents such as Chlorpropamide, Tolbutamide and tolazamide are still in use but are less potent than the second generation drugs like glibenclamide, glipizide and glimepiride. Sulfonylureas are mostly subjected to hepatic metabolism, yielding less active or inactive metabolites that are then eliminated through the kidneys. Patients with impaired hepatic or renal function risk severe hypoglycemia because of accumulation of active drug in circulation. Although these drugs are useful in the treatment of T2DM, their long-term use may lead to a variety of adverse effects, including hepatotoxicity, weight gain, edema and indigestion. Thus there remains an urgent need to develop new antidiabetic agents with higher efficacy and lower toxicity for the long term treatment of T2DM. Much has been published on the characteristics of type 2 diabetes mellitus and its association with the epidemic of obesity. [8]

Search for new, safer anti-diabetic agents are still a challenge for medicinal chemists. From the detailed study of literature review [9-18] and study, we have decided to design and synthesis of novel antidiabetic agents. In the course of our previous work, we observed that various derivatives of sulfonylurea and guanidine possess remarkable antidiabetic activity.

3. Definition of the Problem

Hui-bin Zhang et. al. has reported1-(4-(2-(4-substituted phenylsulfonamido)ethyl)phenylsulfonyl)-3-(4-substitutedxyphenyl)thiourea/urea derivatives with benzenesulfonamide groups as potential hypoglycemic agents. [18] Abbas Ahmadi et. al. has reported synthesis and investigating hypoglycemic and hypolipidemic activities of some glibenclamide analogues in rats. [19] With detailed studies of literature [18 and 19] we have decided to design, synthesis and *in vivo* biological activity of novel hypoglycemic agents

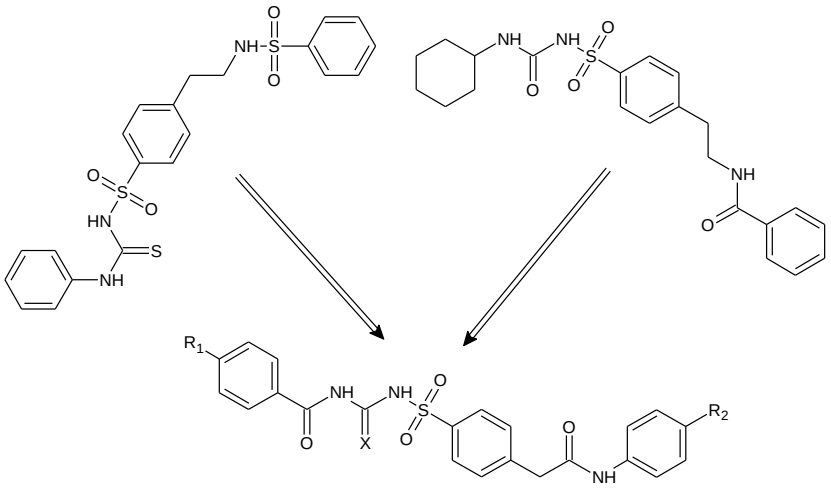


Fig. 1: Design and modification strategies of novel 5a-5q compound

Abbas Ahmadi et. al. has reported Synthesis and Investigating Hypoglycemic and Hypolipidemic Activities of Some Glibenclamide Analogues in Rats.[19] Xun Ji et. al has reported Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2- carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors. [20] We have decided to design, synthesis and *in vivo* biological activity of novel hypoglycemic agents. Design and modification in targeted molecule.

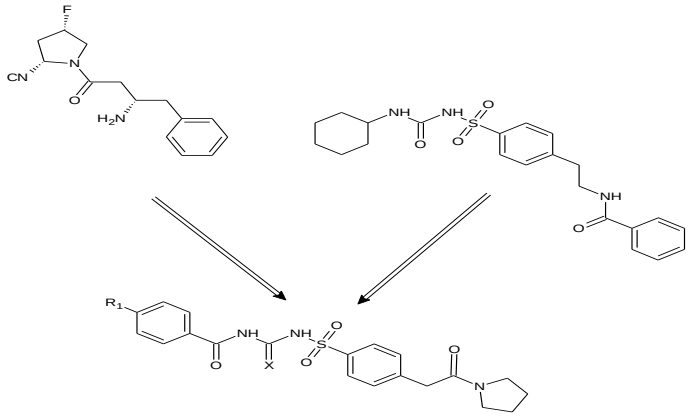


Fig. 2: Design and modification strategies of novel 5r-5w compound

4. Objective and Scope of work

4.1 Objectives:

- Designing of novel hypoglycemic agents with help of literature review and docking studies
- Synthesis of sulphonylureas/guanidine derivatives
- Spectral characterization by IR, MS, ^{1}H NMR and ^{13}C NMR
- *In vivo* Biological evaluation

4.2 Scope of work

The result obtained from in-vitro docking analysis and in-vivo biological activity on rat are significantly same and it can be used as a lead molecule for further development of more potent sulphonylureas /guanidine based derivatives as oral hypoglycemic agents.

5. Original contribution by the thesis

The entire work of design, synthesis novel hypoglycemic agents and biological evolution of same covers basic principles of organic chemistry, medicinal chemistry, molecular modeling, docking studies, and pharmacotherapy helps in reducing micro and macro vascular complication of diabetic patients. It also contributes in developments of novel hypoglycemic agents in the upcoming period.

6. Methodology of Research, Results / Comparisons

6.1 Molecular Docking Study

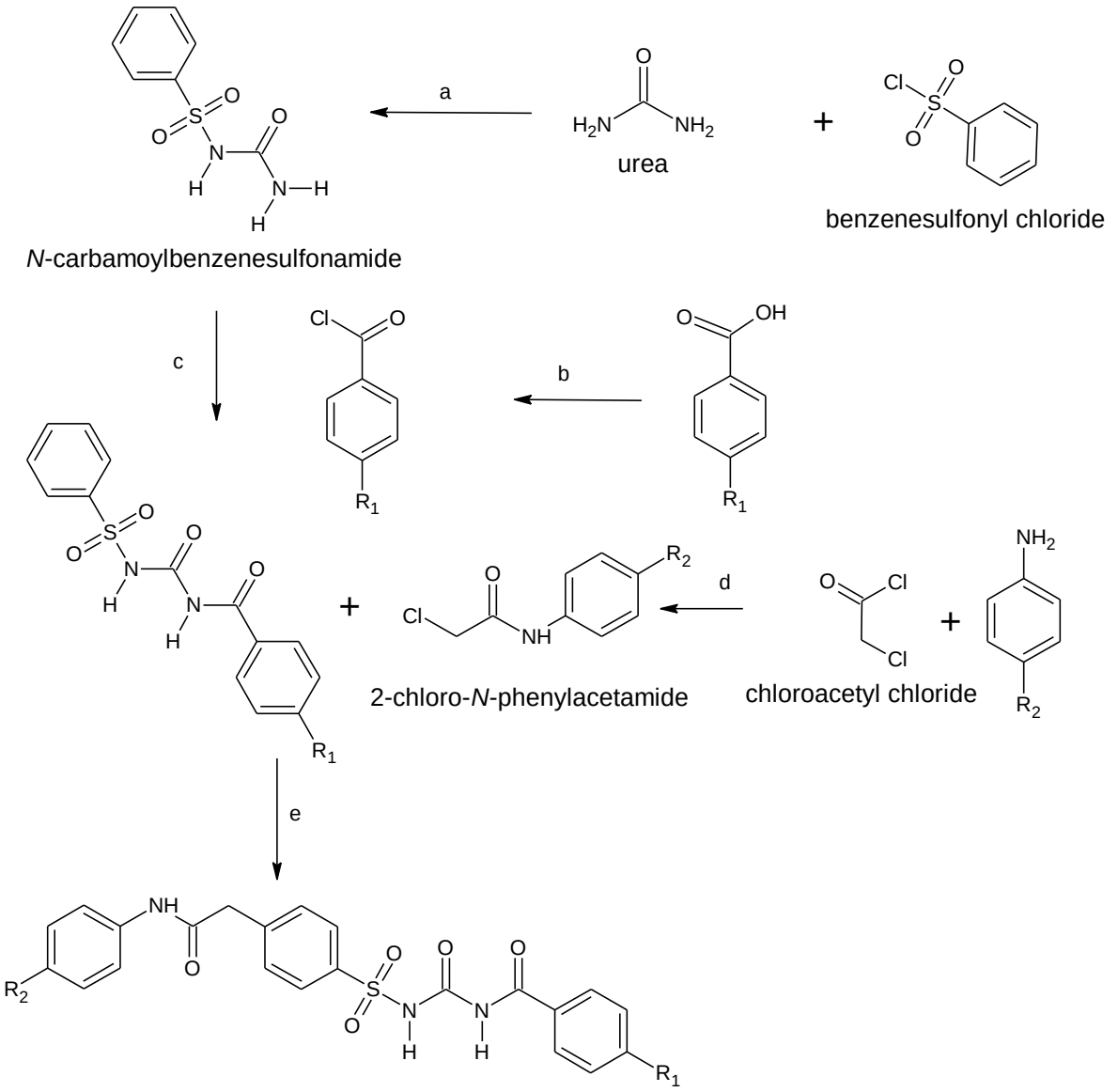
The Crystal structure of the pancreatic ATP-sensitive K^+ channel SUR1/Kir6.2 complexed with ATP and glibenclamide (PDB ID: 5TWV) was imported. [21] Docking, screening and post-analysis of the designed compounds was done using iGEMDOCK program with the protein target 5TWZ. The binding sites of the targets were prepared and the energy minimized compound was imported. During docking, at first the molecules were prepared and bonds, bond orders, explicit hydrogen's, charges, flexible torsions were assigned to both the protein and ligands. From the docking, wizard ligands were selected and the scoring function used was iGEMDOCK score.

The empirical scoring function of iGEMDOCK was estimated as:

Fitness = vdW + Hbond + Elec.

Here, the vdW term is vander Waal energy. H-bond and Elect terms are hydrogen bonding energy and electro-static energy, respectively. The novelty of synthesize compounds ws checked by Sci Finder report. [22]

6.2 Scheme of Synthesis



Scheme 1. Synthetic route for the preparation of the sulphonylureas/gaunidine derivatives: Reagents and conditions: (a) TEA,CH_3CH_2OH,Reflux (yield >75%); (b) $SOCl_2$,reflux,3 h,(yield >60%); (c) TEA,CH_3CH_2OH,Reflux (yield >80%); (d) DRY THF,0 TO RT,Stirring,4 h, rt (yield >85%).(e) Nitrobenzene, $FeCl_3$,reflux,6 h(yield >45%)

Scheme 1 gives synthetic routes of design compounds.

6.3 Chemicals and methods

All the chemicals & reagents collected were of LR grade from Sigma Alderich &Loba Chemie. The reactions were monitored by thin layer chromatography on TLC silica gel 60 F254 plates for completion of the reaction; mobile phase solvents were selected as n-hexane: ethyl acetate (7:3). Melting points of all the synthesized compounds were checked in capillary tubes by using a melting point apparatus (VEEGO melting point apparatus).

All the compounds were characterized by FT-IR spectrometer (Bruker); ^{1}H NMR,^{13}C NMR spectra were obtained from 400 MHz NMR Spectrometer (BrükerBiospin, Switzerland) CoE Rajkot, Gujarat. Mass spectroscopy was performed in Mass spectrophotometer in o2h discovery, Ahmedabad**.**

6.3 Results

6.3.1 Synthesis of 1-Cyclohexanecarbonyl-3-(4-(2- (pyrazine-2-carboxamido) ethyl)phenylsulfonyl)guanidine(5a)

Reflux between N-(2-chloroethyl) pyrazine-2-carboxamide (0.1 mole) and 1-cyclohexanecarbonyl-3-(phenylsulfonyl) guanidine (1 moles) is done for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and liquid of 1-cyclohexanecarbonyl-3-(phenylsulfonyl) guanidine was isolated. The final product was obtained in a yield of 60% with boiling point: 100-102°C. R_f value: 0.4 (mobile phase: ethyl acetate: hexane: 0.7:0.3 IR (cm^{-1}) (KBr): 1727 (C=O)*str*, 3416 (N-H)*str*, 1660 (C=O) *str*, 2988 (C-H), 1292 (S=O) *str*, 2788 (C-H)*str* Ar. MS (m/z): 459 [M+1], ^{13}C NMR (δ ppm), 39.54 ($\underline{C}H_2CH_2Ar$), 38.28 ($CH_2\underline{C}H_2$, Ar), 141.12-145.05 (CH, pyrazine)

6.3.2 Synthesis of 1-(4-(2-Benzamidoethyl) phenylsulfonyl)- 3-(cyclohexane carbonyl) urea (5b)

Reflux of N-(2-chloroethyl)benzamide (0.1mole) and 1-cyclohexanecarbonyl-3-(phenylsulfonyl)urea(0.1 mole) was performed for 7 hours in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid white crystals were isolated with a yield of 75%. m.p: 220-222°C. Rf value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}) (KBr): 1714 (C=O) *str*, 2977 (C-H), 1289 (S=O) *str*, 2976 (C-H) *str*. MS (m/z): 454[M-2], ^{1}HNMR (δ ppm) 2.31 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 1.32 (s, 11H, CH_2) Cyclohexane, 8.16 (s, 1H, NH), 8.16-8.33(m, 9H, ArH)

6.3.3 1-(4-(2-(3-Fluorophenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)urea (5c)

Fridal craft alkylation of 1-(4-nitrobenzoyl)-3-(phenylsulfonyl)urea(0.1 mole) and 2-chloro-N-(3-fluorophenyl)acetamide(1 mole) was done for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and crystals were isolated.

Yield: 65%;m.p: 116-118°C. IR (cm^{-1}) (KBr):3274(N-H),1724(C=O),1625(C-H),3101(C-H) *str* Ar,1157(S=O),1375(NO_2) *str*,1568(NO_2) *str*,1102(C-F); MS (m/z): 500[M+1]; ^{1}H NMR (δ ppm): 3.45(s,2H,CH_2),2.50(s,1H,NH),7.98(s,1H,NH),7.65(d,2H,ArH),7.16(d,2H,ArH),7.60(d,6H,ArH),8.20(d,2H,ArH); ^{13}C NMR (DMSO):157.04(s,C-F),38.81-40.07(t,CH_2-Ar),164.53(s, CONH),115.31-134.88(m, CH-Ar)

6.3.4 1-Benzoyl-3-(4-(2-(3-chlorophenylamino)-2-oxoethyl) phenylsulfonyl) urea(5d)

Reflux of 2-Chloro-N-(3-chlorophenyl)acetamide(1 mole) and 1-benzoyl-3-(phenylsulfonyl)urea(1 mole) was performed for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid white crystals were isolated with yield of 72%.m.p: 112-114 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3). IR (cm^{-1}) (KBr):3361(N-H) *str str*,1638(C=O) *str*,1474(C-H),2974(C-H),1170(S=O) *str*,849(C-Cl). MS (m/z): 474[M+2]. 1HNMR (δ ppm) 2.31 (s, 2H, CH2), 3.48 (s, 2H, CH_2), 10.41(s,1H,NH),8.32(s, 1H,NH),8.17(s,1H,NH) , 7.85- 7.90(d,4H,ArH), 7.65-7.85(d,4H,ArH), 7.50(s, 1H,ArH),7.52(s,1H, ArH)

6.3.5 1-(4-(2-Benzamidoethyl)phenylsulfonyl)-3-cinnamoyl guanidine(5e)

Reaction between 1-cinnamoyl-3-(phenylsulfonyl)guanidine (0.1mole) and N-(chloromethyl)benzamide (0.1mole) was perform for 6 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid white crystals were isolated with yield of 70%.m.p: 190-192 °C. R_f value: 0.7 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}) (KBr): 3417 (N-H) *str*, 1720 (C=O) *str*, 1583 (C-H), 3064 (C-H), 1276 (S=O) *str*. MS (m/z): 476 [M], ^{1}H NMR: 1.2-1.29(t, 4H, CH_2),4.28(s,3H, NH) 7.96(s,2H,NH),7.950-7.935(d,4H,ArH),7.60-7.61(d,2H,ArH),7.47-7.48(d,4H,ArH), 7.49(s,1H,ArH),

6.3.6 1-(2-Chlorobenzoyl)-3-(4-(2-(4-fluorophenylamino)-2-oxoethyl)phenylsulfonyl)urea(5f)

Fridal craft alkaylation of 1-(2-chlorobenzoyl)-3-(phenylsulfonyl)urea(1 mole) and 2-chloro-N-(4-fluorophenyl)acetamide(1 mole) was done for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid white crystals were isolated with yield of 52%.m.p: 130-132 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}) (KBr):1758(C=O) *str*, 1113(S=O), 748(C-Cl), 1508(C-H), 2994(C-H), 3452(N-H) *str*. MS (m/z): 488[M-1].

^{1}HNMR:3.45(s,2H,CH_2),2.50(s,1H,NH),7.98(s,1H,NH),7.65(d,2H,ArH),7.16(d,2H,ArH),7.60(d,6 H,ArH),8.20(d,2H,ArH). ^{13}C NMR ($CDCl_3$):157.04(s, CF), 38.81-40.07(t, CH_2-Ar), 164.53(s, CONH), 115.31-134.88(m, CH-Ar)

6.3.7 1-(2-Chlorobenzoyl)-3-(4-(2-(4-fluorophenylamino)-2 oxoethyl)phenylsulfonyl)guanidine(5g)

Fridal craft alkaylation of 1-(2-chlorobenzoyl)-3-(phenylsulfonyl)guanidine(1 mole) and 2-chloro-N-(4-fluorophenyl)acetamide(1 mole) was done for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid grey crystals were isolated with yield of 47%.m.p: 140-142 °C. R_f value: 0.4 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}

^{1}) (KBr):1738(C=O) *str*, 1158 (S=O), 750(C-Cl), 1509(C-H),2985(C-H) *str*,3449(N-H) *str*. MS (m/z): 487 [M-1]. ^{1}H NMR3.45(s,2H,CH2),2.50(s,1H,NH),7.98(s,1H,NH),7.65(d,2H,ArH),7.16(d,2H,ArH),7.60(d,6H,ArH),8.20(d,2H,ArH) ^{13}C NMR ($CDCl_3$):157.04(s, CF),38.81-40.07(t,CH2-Ar),164.53(s, CONH),115.31-134.88(m, CH-Ar)

6.3.8 1-(Benzoyl)-3-(4-(2-(4-fluorophenylamino)-2-oxoethyl)phenylsulfonyl)guanidine (5h)

1-benzoyl-3-(phenylsulfonyl)guanidine(1 mole) and 2-chloro-N-(4-fluorophenyl)acetamide(1 mole) were reacted in 250 ml round bottom flask for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and gray crystals were isolated with yield of 72%.m.p: 140-142 °C. R_f value: 0.7 (mobile phase: ethyl acetate: hexane: 0.7:0.3); IR (cm^{-1}) (KBr): 1717(C=O) *str*,1175 (S=O) *str*,711(C-F),1508(C-H),2983(C-H). MS (m/z): 453[M-1]. ^{1}H NMR: 3.40-3.69(t, 4H, CH_2) 2.51(s,1H, NH),7.98(s,2H,NH),7.33-7.46(d,6H, ArH),7.80-7.89(d,4H,ArH), 7.12(d,2H,ArH), 7.44(s, 1H,ArH),

6.3.9 1-(4-nitrobenzoyl)-3-(4-(2-oxo-2-(phenylamino) ethyl) phenylsulfonyl)urea (5i)

1-(4-nitrobenzoyl)-3-(phenylsulfonyl) urea(1 mole) and 2-chloro-N-phenylacetamide(1 mole)were reacted for 6 hrs in the presence of anhydrous $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid light yellow crystals were isolated with yield of 72%.m.p: 140-142 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}) (KBr): 3235(N-H) *str*,1724(C=O) *str*,1684(C-H),3095(C-H),1170(S=O),1571(NO) *str*.MS(m/z): 480[M-2], ^{1}HNMR:3.40-3.69(t,4H,CH_2),2.51(s,1H, NH),7.98(s,2H,NH),7.46-7.80(d,6H, ArH), 8.15-8.26(d,4H,ArH), 7.22(d,2H,ArH), 7.0(s,1H,ArH)

6.3.10 1-Cyclohexanecarbonyl-3-(4-(3-(4-nitrophenyl)-1-carboxamido ethyl)phenylsulfonyl)guanidine(5j)

1-cyclohexanecarbonyl-3-(phenylsulfonyl)guanidine (1 mole) and N-(2-chloroethyl)-4-nitrobenzamide (1 mole)were reacted for 6 hrs in the presence $FeCl_3$ and nitrobenzene as solvent. Reaction mixture was cooled and solid crystals were isolated with yield of 70%.MP: 140-142 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3) ; IR (cm^{-1}) (KBr):3417(N-H) *str*,1726(C=O) *str*,1608(C-H),3082(C-H) *str Ar*,1529(NO) *str*,2857 (C-H), 1172(S=O);MS(m/z): 503[M+1], ^{1}HNMR:3.40-3.69(t,4H,CH_2),2.51(s,1H, NH),7.98(s,2H,NH),7.46-7.90(d,4H, ArH), 8.15-8.26(d,4H,ArH)

6.3.11 1-benzoyl-3-(4-(2-oxo-2-(piperazin-1-yl)ethyl)phenylsulfonyl)urea(5k)

2-chloro-1-(piperazin-1-yl)ethanone(0.1 mole) and 1-benzoyl-3-(phenylsulfonyl)urea(0.1 mole) were reacted for 7 hrs in the presence of anhydrous $FeCl_3$ and nitrobenzene as solvent.Reaction mixture was cooled and solid crystals were isolated with yield of 70%.m.p: 140-142 °C. R_f value:

0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3) IR (cm^{-1}) (KBr): 1719(C=O) *str str*,1510(C-H),2927(C-H),1275(S=O) *str*,711(C-Cl).MS(m/z):431[M+1].^{1}H NMR: 8.022-8.053(d,4H,ArH), 7.35(d,4H,ArH),1.99(s,2H,NH), 1.11-1.22(t,4H,Piperazine), 1.31-1.77(t,4H,Piperazine).

6.3.12 1-(4-fluorobenzoyl)-3-(4-(2-oxo-2-(piperazin-1-yl)ethyl)phenylsulfonyl)urea(5l)

Fridal craft alkylation of 1-(4-fluorobenzoyl)-3-(phenylsulfonyl)urea(0.1 mole) and 2-chloro-1-(piperazin-1-yl)ethanone(0.1 mole) in the presence of $FeCl_3$ and nitrobenzene. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3); IR (cm^{-1}) (KBr): 1719(C=O) *str*, 1157(S=O) *str*,1175(C-F),1510(C-H),2927(C-H) *str*. MS (m/z):450[M+2]. 1H NMR: 8.022-8.053(d,4H,ArH), 7.35(d,4H,ArH),1.99(s,2H,NH), 1.11-1.22(t,4H,Piperazine), 1.31-1.77(t,4H,Piperazine).

6.3.13 1-(4-(2-(4-chlorophenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-fluorobenzoyl)guanidine(5m)

Fridal craft alkylation of 1-(4-fluorobenzoyl)-3-(phenylsulfonyl)guanidine (0.1 mole) and 2-chloro-N-(4-chlorophenyl)acetamide (0.1 mole) in the presence of $FeCl_3$ and nitrobenzene. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.7:0.3); IR (cm^{-1}) (KBr): 3500(N-H) *str*, 1700(C=O) *str*,1500(C-H),1157(S=O) *str*. MS (m/z):490 (M+2). ^{1}H NMR: 10.41(s,1H,NH) 7.64-7.65(d,4H,ArH),7.18-7.55(d,4H,ArH),8.32(s, 1H,NH),8.17-8.18(d,4H,ArH),4.406(t,2H,CH_2)

6.3.14 1-(2-chlorobenzoyl)-3-(4-(2-(4-fluorophenylamino)-2-oxoethyl)phenylsulfonyl)urea(5n)

Fridal craft alkylation of 2-chloro-N-(4-fluorophenyl)acetamide(0.1 mole) and, 1-(2-chlorobenzoyl)-3-(phenylsulfonyl)urea(0.1 mole) in the presence of $FeCl_3$ and nitrobenzene. IR (cm^{-1}) (KBr):1758(C=O) *str*,1113(S=O) *str*,748(C-Cl),1508(C-H),2994(C-H),3452(N-H). MS (m/z):488(M-1).^{1}H NMR: 3.40-3.69(t,4H,CH_2),2.51(s,1H, NH),7.98(s,2H,NH),7.16-7.17(d,2H, ArH),7.20-7.53(d,4H,ArH),7.54-7.64(d,6H,ArH), 7.66(s,1H,ArH), 7.31(s,1H,ArH); ^{13}C NMR: 157.04(s, C-F),38.81-40.07(t,CH2-Ar),164(s, CONH),115.31-134.88(m, CH-Ar)

6.3.15 1-(2-Chlorobenzoyl)-3-(4-(2-(4-fluorophenylamino)-2 oxoethyl)phenylsulfonyl)guanidine(5o)

Fridal craft alkylation of 1-(2-chlorobenzoyl)-3-(phenylsulfonyl)guanidine(0.1 mole) and 2-chloro-N-(4-fluorophenyl)acetamide(0.1 mole) in the presence of $FeCl_3$ and nitrobenzene. IR (cm^{-1}) (KBr):1738(C=O) *str*,1158(S=O) *str*,750(C-Cl),1509(C-H),2985(C-H),3449(N-H). ^{1}H NMR: 3.40-3.69(t,4H,CH_2),2.51(s,1H, NH),7.98(s,2H,NH),7.16-7.17(d,2H, ArH),7.20-7.53(d,4H,ArH),7.54-7.64(d,6H,ArH), 7.66(s,1H,ArH), 7.31(s,1H,ArH); ^{13}C NMR: 157.04(s, C-F),38.81-40.07(t,CH2-Ar),164(s, CONH),115.31-134.88(m, CH-Ar).

6.3.16 1-(4-(2-(4-Chlorophenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)urea(5p)

Fridal craft alkylation of 1-(4-nitrobenzoyl)-3-(phenylsulfonyl)urea(0.1 mole) and 2-chloro-N-(4-chlorophenyl)acetamide were done in the presence of $FeCl_3$ and nitrobenzene. IR (cm^{-1}) (KBr):

3415(N-H) *str*, 1717(C=O) *str*,1684(C-H),3080(C-H),1103(S=O),1525(NO) *str*. ^{1}H NMR: 3.40-3.69(t,4H,CH_2),2.51(s,1H, NH),7.98(s,2H,NH),7.16-7.17(d,2H, ArH),7.20-7.53(d,4H,ArH),7.54-7.64(d,6H,ArH), 7.66(s,1H,ArH), 7.31(s,1H,ArH); ^{13}C NMR: 157.04(s, C-F),38.81-40.07(t,CH2-Ar),164(s, CONH),115.31-134.88(m, CH-Ar).

6.3.17 1-(4-nitrobenzoyl)-3-(4-(2-oxo-2-(piperazin-1-yl)ethyl)phenylsulfonyl)guanidine(5q)

Reaction between 1-(4-nitrobenzoyl)-3-(phenylsulfonyl)guanidine(0.1 mole) and 2-chloro-1-(piperazin-1-yl)ethanone(0.1 mole) were performed in the presence of $FeCl_3$ and nitrobenzene. IR (cm^{-1}) (KBr): 3453(N-H) *str*,1640(C=O)*str*,1045(S=O),1378(NO)*str*,1527(NO) *str*;^{1}H NMR: 8.022-8.053(d,4H,ArH), 7.35(d,4H,ArH),1.99(s,2H,NH), 1.11-1.22(t,4H,Piperazine), 1.31-1.77(t,4H,Piperazine).

General procedure for Synthesis of 1-(4-substitutedbenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea/gaunidine (5r-5w)

They were prepared by following the literature method. [23]

Fridalcraft alkylation of 1-(4-substitutedbenzoyl)-3-(phenylsulfonyl)urea/gaunidine (0.1 mmol) and 2-chloro-1-(pyrrolidin-1-yl)ethanone (1 mmol) was done for 7 hrs in the presence of $FeCl_3$ and nitrobenzene as solvent. A reaction mixture was cooled and washes with ice cold water. Solid product was Recrystalize with rectified spirit.

6.3.18 1-(4-Methoxybenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea(5r)

Yield: 65%,m.p 150-152 °C; R_f = 0.75 (ethyl acetate: hexane 2:8 v/v) IR (KBr) (cm^{-1}): 3408(N-H) *str*,2850(C-H),1695(C=O) *str*.MS (m/z): 445[M+]^{1}H NMR (DMSO): δ (ppm)3.76(s,3H,OCH_3),7.87(d,4H,ArH),7.21(d,4H,ArH),10.18(s,1H,NH),2.34(t,4H,Pyrrolidine), 3.39(t,4H, Pyrrolidine)

1-(4-Fluorobenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea(5s)

Yield: 75%; gray crystalline powder; m.p=124-126ºC;R_f = 0.75 (ethyl acetate: hexane 2:8 v/v) IR (cm^{-1})(KBr):3263(N-H),2973(C-H),1672(C=O) *str* ,1378(S=O),1150(C-F);MS(m/z); 435(M+2);^{1}HNMR(DMSO):δ(ppm)7.87 (d, 4H, ArH), 7.25 (d, 4H, ArH), 10.03 (s, 1H, NH),2.14(t,4H,Pyrrolidine), 3.48(t,4H, Pyrrolidine)

1-(4-Nitrobenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea(5t)

Yield: 75%; yellow crystalline powder; m.p=160-164ºC; R_f = 0.60 (ethyl acetate: hexane 2:8 v/v) IR (cm^{-1}) (KBr): 3449(N-H) *str*,2989(C-H),1680(C=O) *str* ,1187(S=O),1549 and 1318(N-O str),^{1}HNMR(DMSO):δ(ppm)7.67 (d, 4H, ArH), 7.20 (d, 4H, ArH), 10.23 (s, 1H, NH),2.17(t,4H,Pyrrolidine), 3.28(t,4H, Pyrrolidine)MS: m/z: 460 [M+]

1-Benzoyl-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea(5u)

Yield: 65%;m.p: 116-118°C.R_f = 0.60 (ethyl acetate: hexane 3:7 v/v) IR (cm^{-1}) (KBr): 3274(N-H) *str*,2993(C-H),1724(C=O) *str*,1102(S=O) *str*; MS:(m/z): 415[M+]; ^{1}H NMR(δ ppm):7.25 (d, 4H, ArH),7.49(s,1H,ArH),7.89 (d, 4H, ArH),2.17(t,4H,Pyrrolidine), 3.28(t,4H, Pyrrolidine)

1-(4-Chlorobenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)urea(5v)

Yield: 70%; m.p=122-126 °C. R_f value: 0.5 (ethyl acetate: hexane: 0.7:0.3). IR (KBr) (cm^{-1}):3363(N-H) *str*,2975(C-H),1682(C=O) *str* ,1378(S=O) *str*,850(C-Cl); MS (m/z): 452[M+2];^{1}HNMR (δ ppm) 7.87 (d, 4H, ArH), 7.25 (d, 4H, ArH), 10.03 (s, 1H, NH),2.14(t,4H,Pyrrolidine), 3.48(t,4H, Pyrrolidine)

1-(4-Nitrobenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenylsulfonyl)guanidine(5w)

Yield: 70%; yellow crystalline powder; m.p=160-164ºC; R_f = 0.6 (ethyl acetate: hexane 2:8 v/v) IR (KBr) (cm^{-1}): 3449(N-H) *str*,2989(C-H),1680(C=O) *str* ,1187(S=O),1575 and 1336(N-O) *str*,^{1}HNMR(DMSO):δ(ppm)7.67 (d, 4H, ArH), 7.20 (d, 4H, ArH), 10.23 (s, 1H, NH),2.17(t,4H,Pyrrolidine), 3.28(t,4H, Pyrrolidine),MS(m/z): 459.2 [M+]

General procedure for Synthesis of 1-(4-substitutedbenzoyl)-3-(4-(2-(4-methoxyphenylamino)-2-oxoethyl)phenylsulfonyl)urea (5x-5J) were prepared by following the literature method. [23]

1-(4-(2-(4-Methoxyphenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)gaunidine (5x)

Yield: 60%; m.p=144-146 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.3:0.7);IR (KBr) (cm^{-1});3449(N-H) *str*,2989(C-H),1684(C=O) *str* ,1187(S=O),1554 and 1320(N-O);MS(m/z):510.8[M-1];^{1}HNMR (δ ppm):7.69 -7.21(d,4H,ArH),8.18-8.206(d,4H,ArH), 10.24(s,1H,NH),3.76(s,3H,OCH_3),3.062(s,2H,CH_2)

1-Benzoyl-3-(4-(2-(4-methoxyphenylamino)-2-oxoethyl)phenylsulfonyl)urea (5y)

Yield: 42%;m.p=114 °C. R_f value: 0.5 (mobile phase: ethyl acetate: hexane: 0.3:0.7); IR (KBr) (cm^{-1}):3449(N-H) *str*,2989(C-H),1688(C=O) *str* ,1187(S=O);MS(m/z):468 [M+1];^{1}HNMR (δ ppm) :7.69-7.21(d,4H,ArH),8.18-8.206(d,4H,ArH), 10.24(s,1H,NH),3.76(s,3H,OCH_3),3.062(s,2H,CH_2)

1-(4-((4-Methoxyphenyl)carbamoyl)phenylsulfonyl)-3-(4-fluorobenzoyl)urea (5z)

Yield: 42%;M. P=84°C. R_f value: 0.55 (mobile phase: ethyl acetate: hexane: 0.3:0.7); IR (KBr) (cm^{-1}):3439(N-H) *str*,2989(C-H),1670(C=O) *str*,1187(S=O);Mass (m/z):471[M+1];^{1}H NMR (δ ppm) :7.69-7.21(d,4H,ArH),8.18-8.206(d,4H,ArH), 10.24(s,1H,NH),3.76(s,3H,OCH_3),3.062(s,2H,CH_2)

1-(4-Chlorobenzoyl)-3-(4-(2-(4-methoxyphenylamino)-2-oxoethyl)phenylsulfonyl)urea(5aa)

Yield: 42%;R_f value: 0.55 (mobile phase: ethyl acetate: hexane: 0.3:0.7); IR (KBr) (cm^{-1}):3352(N-H) *str*,2949(C-H),1690(C=O) *str*,850(C-Cl),1167(S=O) *str*;MS (m/z):503[M+1];^{1}H NMR (δ ppm) :7.69-7.21(d,4H,ArH),8.18-8.206(d,4H,ArH), 10.24(s,1H,NH),3.76(s,3H,OCH_3),3.062(s,2H,CH_2)

***6.4 In-vivo* Biological Evaluation**

Preparation of diabetic animals

Rats of Wistar strain were procured form the Animal House, Department of Pharmacology, Parul institute of pharmacy, Parul University, Vadodara were used in this study. Experiments were carried out in male rats weighing between 150 g and 200 g. They were housed (six per cage) in plastic cages (47cm×34cm×18cm) lined with husk renewed every 24 h. The rats were fed on a pellet diet (Hindustan Lever, India). Drinking water was allowed *ad-libitum*. The animals were housed under standard laboratory conditions maintained at 25±10^{o}C and under 12/12 hour light/dark cycle. The experimental protocol was approved by the institutional animal ethics committee (Protocol No: PIPH 03/16) and by the animal regulatory body of the Indian Government (Registration No: 921/PO/EReBi/S/05/CPCSEA/PIPH03).

6.4.1 Statistical Analysis

Measurement data were tabulated as means±S.E.M. Comparisons were carried out using one way analysis of variances (ANOVA) followed by post-hoc Tukey test and p-value<0.01 as the level of significance. Data was analyzed using the Graph Pad Prism 5.3, San Diego, CA. Figure-4 shows the biological activity of synthesized compounds. Table-3 gives drug and % reduction in Plasma Glucose level (Mean±SEM).

7. Achievements with respect to objectives

7.1 Molecular docking studies

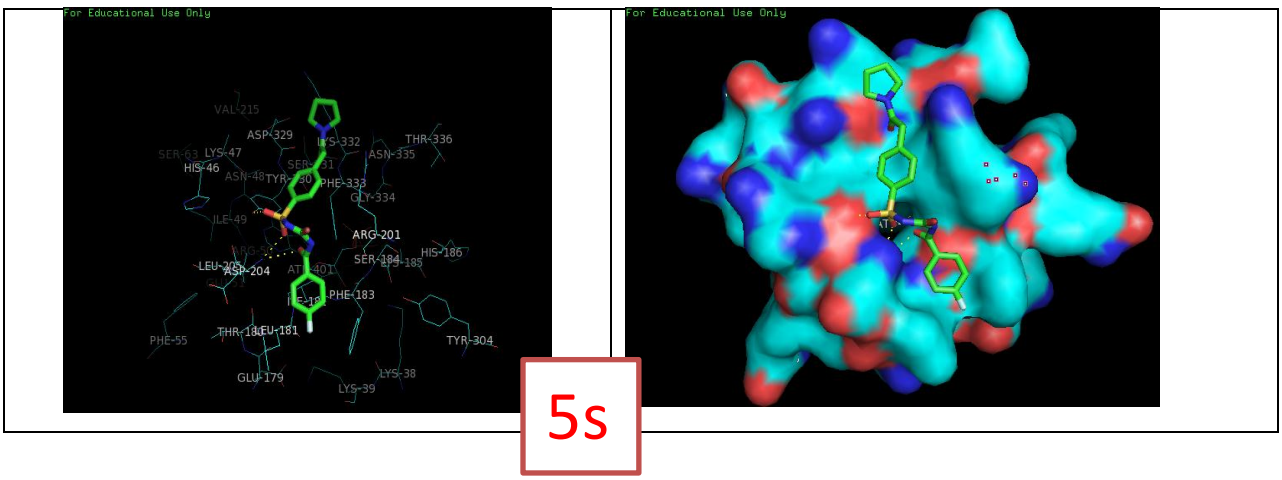
The results were obtained as docking score, i.e. binding energy which is mentioned in **Table-1**.The entire designed compound has shown a good binding affinity in comparison with standard glibenclamide, out of this Compound 5c, 5n, 5f, 5i, 5p and 5z showed better binding affinity in comparison with glibenclamide. Binding cavity and interaction with the various amino acid residues with the compound 5s and 5z were shown in **Figure-3**.

***7.2 In-silico* toxicity studies:**

In-silico toxicity profile of designed compounds was performed using SWISS ADME programme. The Lipnski rule of five was applied. The acceptability of analogues based on Lipinski's rule of five which was essential to ensure drug like properties. The results of *in-silico* toxicity studies mentioned in **Table-2.**

Table 1: Docking results of the designed compounds

Code	Docking score	H- bond energy	Vander Waal energy
5a	-112.311	- 16.3875	-95.9239
5b	-105.994	-13.5407	-92.4534
5c	-120.836	-23.6739	-97.1619
5d	-117.585	-17.7774	-99.8077
5e	-114.053	-15.1444	-98.9087
5f	-129.498	-17.2181	-112.28
5g	-109.071	-9.57071	-99.5003
5h	-119.895	-10.5	-109.395
5i	-120.41	-12.5227	-107.887
5j	-108.041	-35.4247	-73.5922
5k	-105.871	-8.52901	-97.3424
5l	-106.453	-21.6474	-84.8055
5m	-114.529	-20.3845	-94.145
5n	-124.972	-13.2616	-111.71
5o	-112.428	-10.2911	-102.137
5p	-123.115	-16.6997	-105.665
5q	-116.077	-25.9192	-90.1581
5r	-104.667	-95.0936	-19.5733
5s	-108.3982	-86.3291	-13.0691
5t	-104.018	-71.8192	-33.386
5u	-99.6336	-90.4049	-9.22871
5v	-102.399	-91.801	-10.5978
5w	-107.77	-89.3005	-19.6134
5x	-114.205	-82.6018	-23.6027
5y	-112.783	-94.8273	-17.9556
5z	-118.063	-105.333	-12.7301
5aa	-104.372	-98.9745	-5.39719
Glibenclamide	-108.996	-91.48	-17.5158



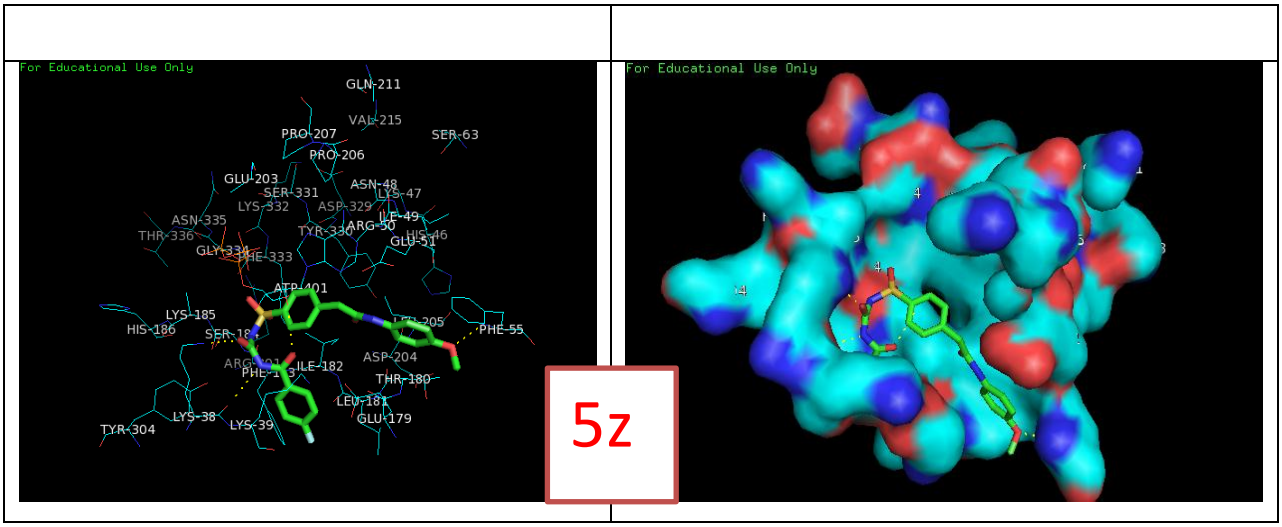


Figure-3 Binding pocket and interaction with various residues of compound 5s, 5z

Table 2: *In-silico* toxicity studies

Compound code	Mol. wt (g/mol)	HBd	HBa	C Log P	Drug likeness
5a	459	**4**	**7**	**2.15**	Yes, 0 violations
5b	457	3	5	2.91	Yes, 0 violations
5c	500	4	5	2.20	Yes, 0 violations
5d	471	3	5	2.88	Yes, 0 violations
5e	476	4	6	2.88	Yes, 0 violations
5f	489	3	6	3.17	Yes, 0 violations
5g	488	4	6	3.60	Yes, 0 violations
5h	454	4	6	2.88	Yes, 0 violations
5i	484	4	7	1.803	Yes, 0 violations
5j	502	5	7	3.591	Yes, 1 violation
5k	430	3	6	1.621	Yes, 0 violations
5l	448	3	7	1.7	Yes, 0 violations
5m	488	3	7	3.60	Yes, 0 violations
5n	489	3	6	3.17	Yes, 0 violations
5o	489	4	6	3.60	Yes, 0 violations
5p	517	4	7	2.77	Yes; 1 violation
5q	475	5	8	1.793	Yes, 0 violations
5r	445	2	6	1.70	Yes, 0 violations
5s	433	2	6	1.91	Yes, 0 violations
5t	461	3	7	0.33	Yes, 0 violations
5u	415	2	5	1.68	Yes, 0 violations
5v	449	2	5	2.11	Yes, 0 violations
5w	460	7	10	0.18	Yes, 0 violations
5x	513	4	8	0.48	Yes, 1 violation
5y	467	3	6	2.32	Yes, 0 violations
5z	485	3	7	2.65	Yes, 0 violations
5aa	501	3	6	2.85	Yes, 0 violations

7.3 Biological evaluation

Blood data analysis was done by graph pad prism one way ANOVA followed by turkey test. In our study, we have found that administration of compounds 5a-5aa to diabetic rats reversed their blood glucose. The possible mechanism by which they brings about them hypoglycemic action may be

by potentiation of the insulin effect of plasma by increasing either the pancreatic secretion of insulin from β-cells of islets of Langerhans or its release from the bound form. However, the Compound 5c, 5d, 5f, 5i, 5n, 5p, 5z shows better % reduction of blood glucose level (Table no 3 and Figure-4) compares to other derivatives. **5c** contain electron withdrawing NO_2 in the 4^{th} position of benzene ring which has significant effects on blood sugar reduction.

Table 3: *In-vivo* hypoglycemic activity of compounds 5a-5aa

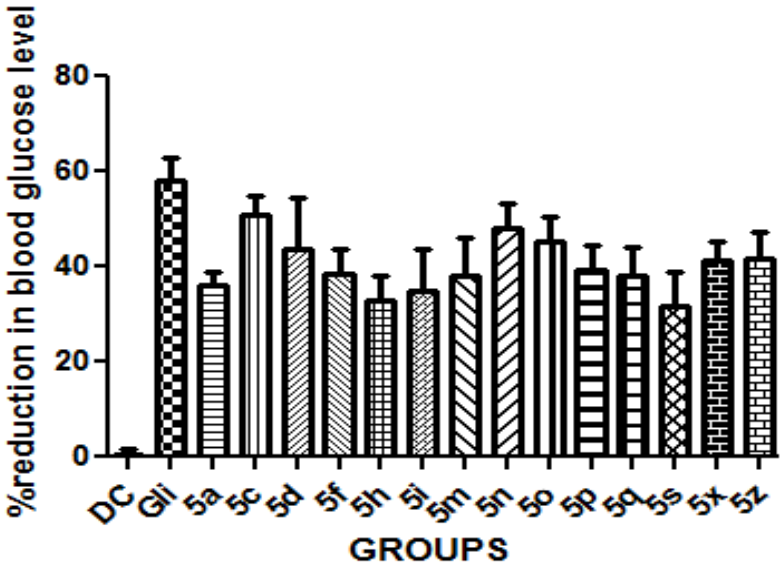
Groups	Mean±S.E.M
DC	0.6287±0.9512
GLI	57.89±4.905
5a	35.91±2.9
5c	50.88±3.7
5d	43.72±10.6
5f	38.57±5.1
5h	32.81±5.3
5i	35.02±8.7
5m	37.97±8.02
5n	47.93±5.4
5o	45.27±5.2
5p	39.13±5.1
5q	38.04±6.024
5s	31.66±7.02
5x	41.39±3.7
5z	41.52±5.9

Values are given as mean±S.D. for six rats in each group.

Experimental groups are compared with Glibenclamide.

Values are statistically significant at $^{**}P < 0.01$ as compared with diabetic control

Figure 3: BIOLOGICAL ACTIVITY STUDIES OF THE SYNTHESIZED DERIVATIVES



8. Conclusion

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work, in the binding and interactions of sulphonylureas/guanidine derivatives with ATP-sensitive K^+ channel SUR1/Kir6.2 complexed with ATP and glibenclamide (PDB ID: 5TWV) was imported have been studied using molecular docking. Most of the compounds have shown significant binding interactions for same. It was observed that the benzene ring, F, NO_2 group, sulphonamide group is an important. However, the Compound 5c, 5d, 5f, 5i, 5n, 5p, 5z shows better % reduction of blood glucose compares to other derivatives. So, the 4^{th} and 2^{nd}positions of derivatives substituted with F, NO_2, and Cl which was shown better result compare to unsubstituted or substituted with other derivatives.

9. Copies of papers published and a list of all publications arising from the thesis

Sr.No.	Author/S	Title of the Paper	Journal/Publication	Details 0f Journal (Vol., Issue, Page No.)
1	Ishan I. Panchal,Dhrubo Jyoti Sen, Samir K. Shah	Synthetic Approach Towards Some Substituted Sulphonylureas And Guanidine Derivatives As Hypoglycemic Agents	European Journal of Pharmaceutical and Medical Research	ejpmr, 2016,3 (3), 433-442
2	Dhrubo Jyoti Sen, Ishan I. Panchal, Ashish D. Patel	Scifinder® As A Latest Tool In Innovative Research Within A New Dimension For Integrating Scientific Chemical Databases	European Journal of Pharmaceutical and Medical Research	ejpmr, 2016,3(11), 01-19
3	Ishan I. Panchal, Dhrubo Jyoti Sen, Samir K. Shah	Novel Approach In Diabetes Mellitus: Say No To Sugar And Yes To Artificial Sweeteners	International Journal of Pharmaceutical Research and Bio-Science	ijprbs, 2014; Volume 3 (2): 770-784
4	Ishan I. Panchal, Dhrubo Jyoti Sen, Bhavesh Prajapati,Samir K. Shah	Serendipity of Fluorine In Discovery And Development Of Antidiabetic Agents: A Bottleneck Systemic Review	World Journal of Pharmaceutical Sciences	World J Pharm Sci 2013; 1 (4): 168-175
5	Ishan I. Panchal, Dhrubo Jyoti Sen, alkesh K. Patel,Samir K. Shah	Leptin Centered Therapy For Diabetes: Great Hope For Imminent	World Journal of Pharmacy and Pharmaceutical Sciences	World J Pharm And Pharma Sci 2013;3 (1), 795-806.
6.	Ishan Panchal, Dhrubo Jyoti Sen, Umang Shah, Archana Navale	Structure Based Drug Designing, Scoring, And Synthesis Of Some Substituted Sulphonylureas/Guanidine -Based Derivatives As Hypoglycemic Agents	International Journal of Pharmacy And Pharmaceutical Sciences (Elsevier) (**SJR Scimago Journal & Country Rank 0.51)**	In review,
7.	Ishan I Panchal, Dhrubo Jyoti Sen, Ashish Shah, Ashish Patel, Vashisth Bhavsar	Molecular Docking And Synthesis of Some Substituted Sulphonylureas/Pyrrolidine -Based Derivatives as Hypoglycemic Agents	Journal of Chemical and Pharmaceutical Research. SJR(Elsevier) **(SJR Scimago Journal & Country Rank 0.28)**	J Chem Pharma Res, 2017, 9 (8):164-172

8.	Ishan I Panchal, Dhrubo Jyoti Sen, Ashish D Patel, Umang Shah, Mehul Patel, Archana Navle, Vashisth Bhavsar	Molecular Docking, Synthesis And Biological Evaluation Of Sulphonylureas/Guanidine Derivatives As Promising Antidiabetics Agent	Current drug discovery technologies **(SJR, Scimago Journal & Country Rank 1.5) , Scopus (Bentham Science)**	Accepted, September, 2017

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