



Review On Sulfonylureas As Antidiabetic Agent

Shraddha Chitale*, Dr. Ramesh Sawant

P. D. V. V. P. Foundation College of Pharmacy, Vilad ghat, Ahmednagar,
Maharashtra.

Abstract-

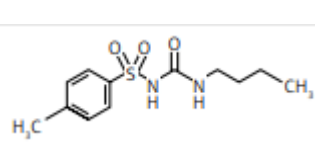
Many anti-diabetic drugs with different mechanisms of action are now available for treatment of type 2 diabetes mellitus. Sulfonylureas have been extensively used for treatment of type 2 diabetes for nearly 50 years and, even in our times, are widely used for treatment of this devastating chronic illness. Here, we review some of the available data on sulfonylureas, evaluating their mechanism of action and their effects on glycemic control. We can conclude that sulfonylureas are still the most used anti-diabetic agents: maybe this is due to their lower cost, to the possibility of mono-dosing and to the presence of an association with metformin in the same tablet. However, sulfonylureas, especially the older ones, are linked to a greater prevalence of hypoglycemia, and cardiovascular risk; newer prolonged-release preparations of sulfonylureas are undoubtedly safer, mainly due to reducing hypoglycemia, and for this reason should be preferred.

Key words: glycemic control, hypoglycemia, sulfonylureas.

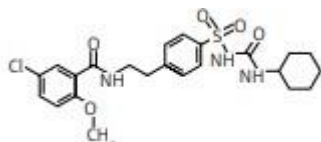
Introduction-

Many anti-diabetic drugs with different mechanisms of action are now available to treat type 2 diabetes mellitus, including sulfonylureas, glinides, thiazolidinediones [1, 2], biguanides [3], and α -glucosidase inhibitors [4, 5]. Recently, incretin-related drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors [6, 7], and glucagon-like peptide-1 (GLP-1) receptor agonists [8, 9], have been developed. Despite the large number of anti-diabetic agents available, however, sulfonylureas remain the most widely used drugs for treating patients with type 2 diabetes [10]. Sulfonylureas were discovered in 1942, when Janbon et al. observed that some sulfonamides generated hypoglycemia in experimental animals. From this observation carbutamide (1-butyl-3-sulfonylurea) was synthesized. Carbutamide was the first sulfonylurea used to treat diabetes, but was subsequently withdrawn from the market because of its adverse effects on bone marrow. By the 1960s several sulfonylureas became available; they are traditionally classified into 2 groups (or generations). Gliclazide, glipizide, glibenclamide and glimepiride are

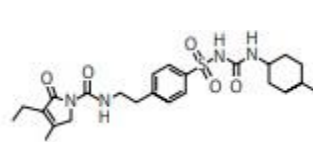
second-generation sulfonylureas, recently used, while first-generation drugs (such as tolbutamide and chlorpropamide) are no longer used.



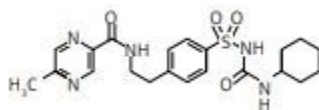
Tolbutamide



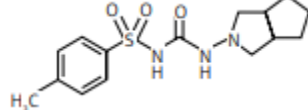
Glibenclamide



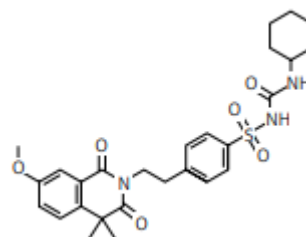
Glimepiride



Glipizide



Glipizide



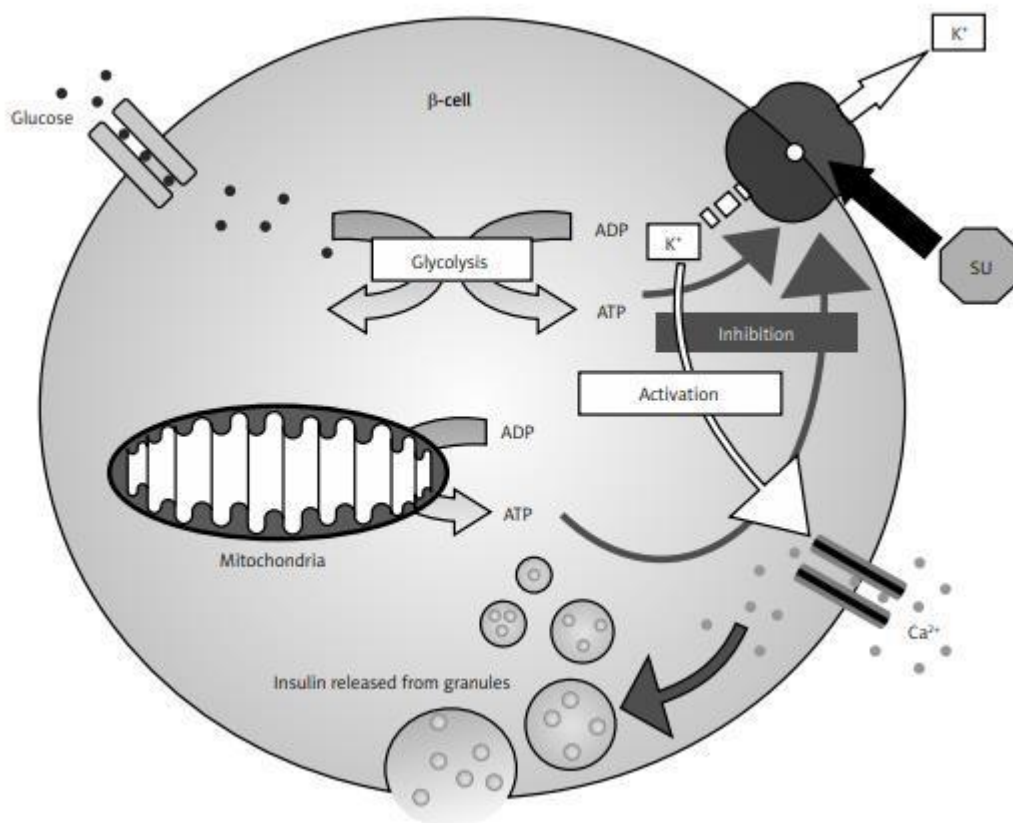
Gliquidone

Second-generation drugs are equally effective in lowering blood glucose concentrations, but there are differences in absorption, metabolism and dosing (Table I). Sulfonylureas should be considered for diabetic patients who are not overweight or those for whom metformin is contraindicated or is not enough to achieve adequate glycemic control [11]. Mechanism of action the main effect of sulfonylureas is the rise in plasma insulin concentrations; consequently, they are effective only when residual pancreatic β -cells are present. The rise in plasma insulin levels occurs for two reasons. Firstly, there is stimulation of insulin secretion by pancreatic β -cells, and secondly, there is a decrease in hepatic clearance of insulin. In particular, this second effect appears mainly after the increase of insulin secretion has taken place. In fact, in the first month of treatment, the levels of insulin and insulin response to glucose rise rapidly, resulting in lowered blood glucose. After this period, baseline and stimulated insulin levels become lower compared to those measured at the beginning of treatment; however, blood glucose values remain unchanged. The reason for this observation is not clear. With regard to the secretory activity of sulfonylureas, the mechanism is now known. They act by binding to the specific receptor for sulfonylureas on β -pancreatic cells, blocking the inflow of potassium (K^+) through the ATP-dependent channel: the flow of K^+ within the β -cell goes to zero, the cell membrane becomes depolarized, thus removing the electric screen which prevents the diffusion of calcium into the cytosol. The increased flow of calcium into β -cells causes the contraction of the filaments of actomyosin responsible for the exocytosis of insulin, which is therefore promptly secreted in large amounts (Figure 1). In particular, the sulfonylureas receptor (SUR1),

a 1581-amino acid protein, has high affinity for glibenclamide. SUR1 is a member of the ATP-binding cassette (ABC) super-family that has two nucleotide binding folds (NBF-1 and NBF-2). Each nucleotide

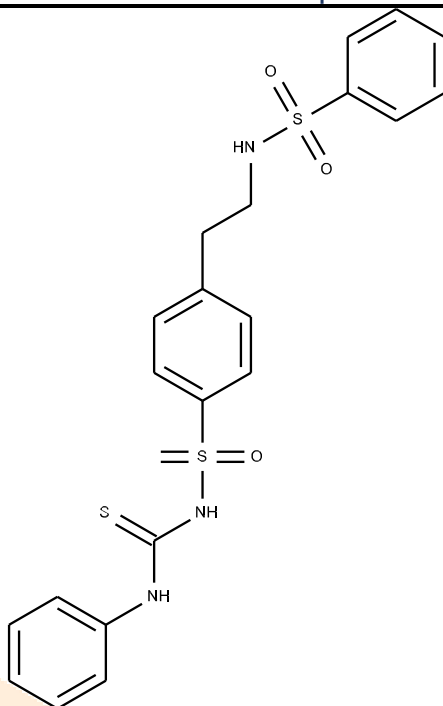
binding fold contains the Walker A and B motifs and the SGGQ ABC signature, and it is important in nucleotide regulation of the functional activities of ABC proteins. SUR1 has three transmembrane domains (TMD), TMD0, TMD1 and TMD2, which consist respectively of 5, 6 and 6 transmembrane (TM) segments that are numerated progressively. TMD0 contains the TM segments from 1 to 5, TMD1 contains the TM segments from 6 to 11, and TMD2 contains the TM segments from 12 to 17. SUR1 is expressed at higher levels in pancreatic islets. SUR1 is also present in the brain. Also a second type of sulfonylureas receptor exists; it is named SUR2A (formerly called SUR2), and it is an isoform of SUR1. SUR2A is a protein of 1545 amino acids sharing 68% amino acid identity with SUR1. SUR2A has a low affinity for glibenclamide. Several variants of SUR2A have also been identified. One of them, SUR2B, differs from SUR2A by 42 amino acids in the C-terminus, where it is, instead, similar to SUR1. Although SUR2A is expressed predominantly in heart and skeletal muscle, SUR2B is expressed widely in other tissues. In the past a two-site model (A site and B site) had been proposed for the interaction between sulfonylureas, glinides and SUR. The A site is located on the eighth (between TM segments 15 and 16) cytosolic loop, which is specific for SUR1.

Instead the B site involves the third (between TM segments 5 and 6) cytosolic loop, which is very similar in all SURs. According to these different sites of interaction, sulfonylureas and glinides can be divided into three groups. The first of these includes nateglinide, tolbutamide and gliclazide, which are molecules that bind specifically the A site of SUR1, while the second group, which includes glimepiride and glibenclamide, binds non-specifically the B sites of both SUR1 and SUR2A as well as the A site of SUR1; finally, the third group (which includes meglitinide and repaglinide) binds to the B site of SUR1 and SUR2A. Beside the “first phase”, sulfonylureas also increase the “second phase” of insulin secretion that begins 10 min later as insulin granules are translocated to the membrane of the β -cell. This second phase involves the progressive formation of new insulin granules, and it is possible only if β -cell function is preserved. It is important to underline that the release of insulin induced by sulfonylureas is independent of glucose levels, and this can increase the risk of hypoglycemia.



Sulfonylthiourea Derivatives as Antidiabetic Activities

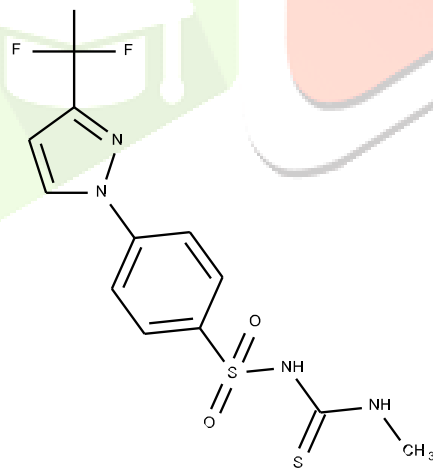
Hui-bin Zhang *et al* in 2009 reported, Sulfonylthiourea derivatives substituted with benzenesulfonamide groups were designed and synthesized. The target compounds were assayed for the effects on the insulin release of isolated rat pancreatic islets and the glucose transport in adipocytes of rats. Some of them exhibited high potency. Compound 10 also had potent antiplatelet activity and showed an excellent property to protect collagen–epinephrine-induced mice mortality as well as plasma glucose-lowering activity in vivo.



Sulfonylthiourea Derivatives Substituted with Benzenesulfonamide Groups

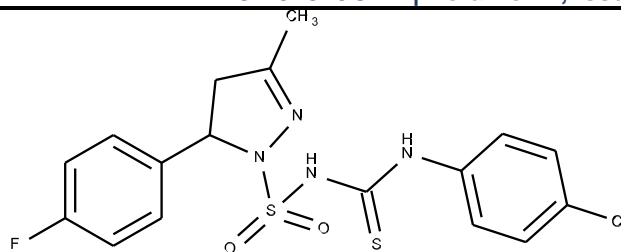
Faidallaha HM *et al* in 2011 reported, synthesized fluorinated pyrazoles, benzene sulfonylurea, and thiourea derivatives as well as their cyclic sulfonyl thioureas analogs as hypoglycemic and antibacterial agents. These compounds 4-oxothiazolidines, 4-oxo-5,6-dihydrothiazine, 5-oxo-4,5-dihydrothiazines and thiazolines revealed significant antidiabetic and antibacterial activities.

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Fluorinated Pyrazoles Sulfonylthiourea Derivative

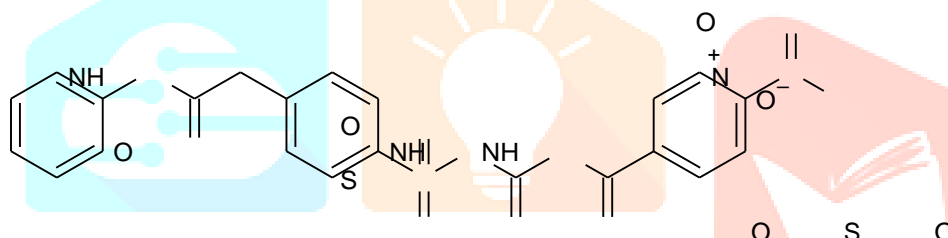
Hassan M. *et al* in 2016 reported, Sulfonylthiourea derivatives were prepared as hypoglycemic agents. A significant attenuation in the biological activity was reported when the sulfonylurea moiety is replaced by sulfonylthiourea as can be seen good hypoglycemic agent.



Sulfonylthiourea Derivative

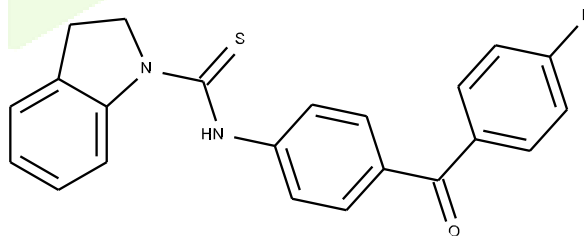
Ishan Panchal *et al* in 2017 reported,

1-(4-(2-(4-Substitutedphenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-substitutedbenzoyl)urea (5A-5B), 1-(4-(2-(4-substitutedphenylamino)-2-oxoethyl)phenylsulfonyl)-3-(4-substituted-benzoyl)guanidine (5C-5E) and, 1-(4-Substitutedbenzoyl)-3-(4-(2-oxo-2-(piperazin-1-yl)ethyl)phenylsulfonyl)urea (5F-5H) based derivatives as hypoglycemic agents. All compounds have shown considerable activity with respect to glibenclamide, but compounds 5D (52.49 ± 7.73) and 5E (48.18 ± 4.22) are equipotent with respect to activity as compared to standard glibenclamide (55.97 ± 3.19).



Substituted Phenyl Sulfonylthiourea Derivative

Dhineshkumar Manoharan *et al* in 2017 reported, antidiabetic activities of all the above indoline derivatives were examined by standard α -amylase inhibition assay. The inhibition efficiency of all synthesized compounds was tested at a concentration ranging from 50 to 250 $\mu\text{g/mL}$.

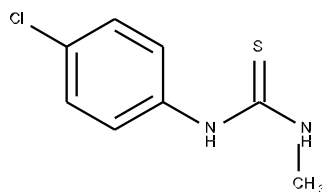


Indoline Sulfonylthiourea derivatives

Tanmoy Guria *et al* in 2018 reported, A series of hybrid urea/thiourea derivatives (5a-5f) with chalcone moiety were synthesized and pharmacological activity was evaluated using *invitro* α -glucosidase inhibition assay and *in vivo* antidiabetic activity in streptozotocin (STZ) induced diabetic rat model. Among the synthesized molecules, compound 5d (1-[4'-N-(N'-p-chlorophenyl)urenyl]phenyl]-3-(4-methoxyphenyl)-2-propen-1-one) is more potent with IC_{50} value 12.88 μM when compared to the standard drug Acarbose (IC_{50} 16.54 μM) in *invitro* study and *in vivo*

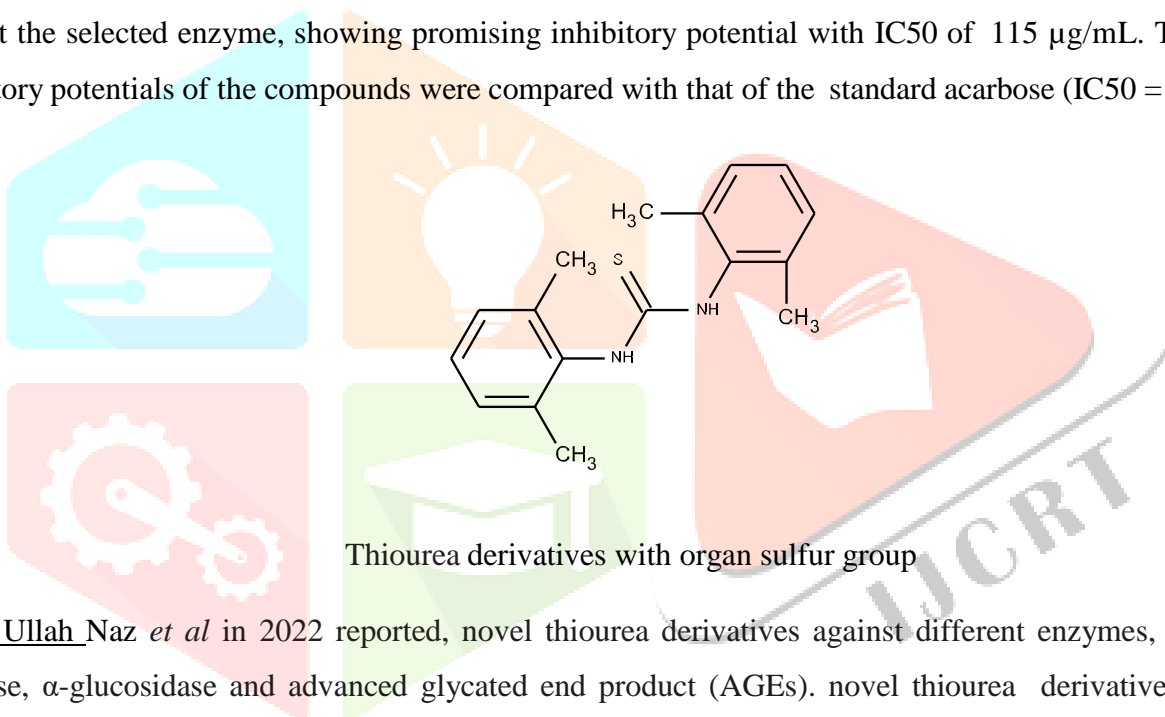
it is potent activity .

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Sulfonylthiourea derivatives with chalcone moiety

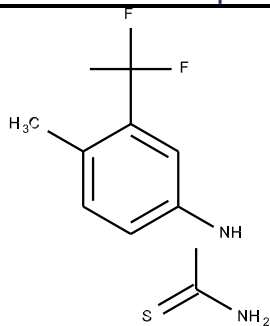
Sumaira Naz *et al* in 2020 reported, Thioureas and their derivatives are organosulfur compounds were screened for in vitro inhibition of α -amylase, α -glucosidase. The derivative was found to be highly potent against the selected enzyme, showing promising inhibitory potential with IC_{50} of 115 μ g/mL. The observed inhibitory potentials of the compounds were compared with that of the standard acarbose ($IC_{50} = 36 \mu$ g/mL).



Thiourea derivatives with organ sulfur group

Amin Ullah Naz *et al* in 2022 reported, novel thiourea derivatives against different enzymes, such as α -amylase, α -glucosidase and advanced glycated end product (AGEs). novel thiourea derivatives showed activity against α -amylase. The corresponding percentage inhibitions were found to be 85 ± 1.9 , 82 ± 0.7 , 75 ± 1.2 , 72 ± 0.4 , and $65 \pm 1.1\%$, respectively. These compounds were then screened using in vitro assays. Among them, AH showed the highest activity against α -glucosidase, AGEs, and PTP1B, with percentage inhibitions of $86 \pm 0.4\%$ ($IC_{50} = 47.9 \mu$ M), $85 \pm 0.7\%$ ($IC_{50} = 49.51 \mu$ M), and $85 \pm 0.5\%$ ($IC_{50} = 79.74 \mu$ M), respectively.

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Novel Thiourea Derivatives

Concluding remarks

Searching for effective and safe drugs has always been a highlight for medicinal researchers, against diabetes and its complications. As T2D accounts for approximately 90% of diabetes, more and more researchers are now focusing on drugs against T2D that can ameliorate insulin resistance, such as insulin sensitizers and insulin mimetics, redress beta-cell function, or improve the incretin system. A recent alternative is to block the reuptake of glucose in the renal tubules by inhibiting SGLT2, promoting the loss of glucose in the urine, thus lowering blood glucose levels.

We have reviewed the antidiabetic effects of coumarins and their potential mechanisms. Plenty of *in vivo* and *in-vitro* evidence demonstrates that coumarins can improve diabetes using antioxidative and anti-inflammatory action, improvement of pancreatic function, and correction of abnormal insulin signaling. They are consequently valuable and should be further researched and developed. In summary, coumarins possess a variety of biochemical and pharmacological properties that may be effective against diabetes and its complications, some of which are of potential therapeutic interest. As the multifactorial pathogenicity of diabetes demands a multimodal therapeutic approach, the diversity of coumarin targets is beneficial for antidiabetic application. Literature indicates that coumarins could be used to treat diabetes and cardiovascular complications or as an auxiliary combined with other antidiabetic agents based on the concept of integrative medicine that combines conventional treatment with evidence-based complementary therapies.

References

1. Derosa G, Maffioli P. Thiazolidinediones plus metformin association on body weight in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2011; 91: 265-13.
2. Derosa G, Tinelli C, Maffioli P. Effects of pioglitazone and rosiglitazone combined with metformin on body weight in people with diabetes. *Diabetes Obes Metab* 2009; 11: 1091-9.
3. Cicero AFG, Tartagni E, Ertek S. Metformin and its clinical use: new insights for an old drug in clinical practice. *Arch Med Sci* 2012; 8: 907-17.
4. Derosa G, Maffioli P. Efficacy and safety profile evaluation of acarbose alone and in association with other antidiabetic drugs: a systematic review. *Clin Ther* 2012; 34: 1221-36.
5. Derosa G, Maffioli P. Alpha-glucosidase inhibitors and their use in clinical practice. *Arch Med Sci* 2012; 8: 899- 906.
6. Derosa G, Maffioli P. Dipeptidyl peptidase-4 inhibitors: 3 years of experience. *Diabetes Technol Ther* 2012; 14: 350-64.
7. Derosa G, Maffioli P. Patient considerations and clinical utility of a fixed dose combination of saxagliptin/ metformin in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes* 2011; 4: 263-71.
8. Derosa G, Maffioli P. GLP-1 agonists exenatide and liraglutide: a review about their safety and efficacy. *Curr Clin Pharmacol* 2012; 7: 214-28.
9. Derosa G, Maffioli P. Optimizing glycemic control: clinical utility of exenatide prolonged release injection. *Res Rep Endocr Disord* 2012; 2: 41-51.
10. Bressler R, Johnson DG. Pharmacological regulation of blood glucose levels in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997; 157: 836-48.
11. American Diabetes Association. Standards of Medical Care in Diabetes-2013. *Diabetes Care* 2013; 36 (Suppl. 1): S11-66.
12. Ramracheya R, Ward C, Shigeto M, et al. Membrane potential-dependent inactivation of voltage-gated ion channels in alpha-cells inhibits glucagon secretion from human islets. *Diabetes* 2010; 59: 2198-208.
13. Braun M, Ramracheya R, Amisten S, et al. Somatostatin release, electrical activity, membrane currents and exocytosis in human pancreatic delta cells. *Diabetologia* 2009; 52: 1566-78.
14. Olefsky JM, Reaven GM. Effects of sulphonylurea therapy on insulin binding to mononuclear leukocytes of diabetic patients. *Am J Med* 1976; 60: 89-95