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Sulfonylurea Review

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HUMAN

Farah Yousef*[1], Oussama Mansour[2], Jehad Herbali[3]

[1] *Ph.D. candidate in pharmaceutical sciences, Damascus University, Damascus, Syria.*

[2] *Assistant Professor in pharmaceutical chimestry, Tishreen University, Lattakia, Syria*

[3] *Assistant Professor in pharmaceutical chimestry, Damascus University, Damascus, Syria.*

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ABSTRACT

Diabetes Mellitus is a chronic disease represented with high glucose blood levels. Although sulfonylurea compounds are the second preferred drug to treat Type II Diabetes (TYIID), they are still the most used agents due to their lower cost and as a mono-dosing. Literature divides these compounds according to their discovery into 1st, 2nd, 3rd generations. However, only six sulfonylurea compounds are now available for use in the United States: Chlorpropamide, Glimepiride, Glipizide, Glyburide, Tolazamide, and Tolbutamide. They function by increasing insulin secretion from pancreatic beta cells. Their main active site is ATP sensitive potassium ion channels; Kir 6.2\SUR1; Potassium Inward Rectifier ion channel 6.2\ Sulfonylurea receptor 1. They are sulfonamide derivatives. However, researchers have declared that sulfonylurea moiety is not the only one responsible for this group efficacy. It has been known that sudden and acute hypoglycemia incidences and weight gain are the two most common adverse effects TYIID the patient might face during treatment with sulfonylurea agents. This review indicates the historical development of sulfonylurea and the differences among this group members.

INTRODUCTION:

Sulfonylurea Background

Sulfonylureas are commonly used in type II diabetes treatment. [1-3] They are often prescribed for diabetic patients who are not of overweight or those for whom metformin is contraindicated or is not enough to achieve adequate glycemia control. Their hypoglycemic activity was first noticed by Ruiz in 1937 when he was doing experiments on sulfa drugs. [4-5] Later on, in 1942, Jabon confirmed this efficacy when anti-bacterial sulfonamide; p-amino-sulfonamide-isopropylthiodiazole, caused hypoglycemic activity as side effect while treating patients for typhoid. Studies on sulfonamide bioactivities expanded as Laboratories proved that sulfa drugs stimulated β-cell release of insulin. [1,4] In 1950s, Carbutamide; 1-butyl-3-sulfonylurea, was the first sulfonylurea compound presented in the clinical use for diabetes therapy, yet not for too long as it had adverse effects on bone marrow. [3] In 1956, Germany introduced tolbutamide; sulfa drugs derivate, as the first sulfonylurea compound to be in clinical use of diabetes treatment. Other first generation sulfonylurea compounds such as acetohexamide, tolazamide, and chlorpropamide were available in the German market. [1-2] Glyburide and glipizide; more potent sulfonylurea members entered the US drug market in 1984; more than a decade of their usage in Europe. [7] Furthermore, Glimepiride, the most potent sulfonylurea compound, was not commercially introduced till 1995 in the US drug market. [8]

Sulfonylurea classification

Researchers divide these compounds according to their discovery into 1st, 2nd, 3rd generations. Tolbutamide, Tolazamide, Acetohexamide, carbutamide, Chlorpropamide, glycyclamide, metahexamide are the first generation, while Glyburide (Glibenclamide), Gliclazide, Glipizide, Glibornuride, Gliquidone, glisoxepide, glyclopyramide Glymidine, are the second generation. Glimepiride represents the third generation. [8]

Sulfonylurea chemically

They are sulfonamide derivates (fig1). The ones that proved hypoglycemic activity are Tolbutamide, Tolazamide, Acetohexamide, carbutamide, Chlorpropamide, glycyclamide, metahexamide, Glyburide (Glibenclamide), Gliclazide, Glipizide, Glibornuride, Gliquidone, glisoxepide, glyclopyramide Glymidine, and Glimepiride. Their chemical structures are presented in fig 2.Chemical properties of sulfonylureas obtained from PubChem and

Diabetes.net are presented in Table1. [9-13] However, only six sulfonylurea compounds are now available for use in the United States: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide. [14]

Table 1: chemical properties of sulfonylurea derivatives

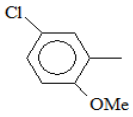
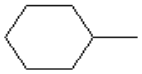
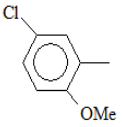
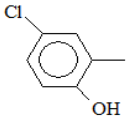
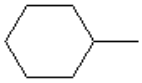
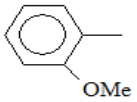
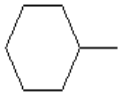
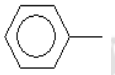
Compound Name	**M. Weight**	**Log P**	**pK_a**	**Hydrogen bond Donner count**	**Hydrogen bond acceptor count**	**Dosage mg\day**	**Rel. potency**	**Generation**
Tolbutamide	270.347	2.3	5.16	2	3	500-3000\2-3	1	First
Tolazamide	311.4	2.69	3.6	2	4	100-1000\1-2	3	
Acetohexamide	324.395	2.3	6.6	2	4	N\A	2.5	
Carbutamide	271.335	1.01	N\A	3	4	N\A	N\A	
Chlorpropamide	276.735	2.2	5.13	2	3	100-500\1-2	6	
Glycyclamide	296.119	N\A	N\A	2	3	N\A	N\A	
Metahexamide	311.4	N\A	3	3	4	N\A	N\A	
Glyburide	494.003	4.9	N\A	3	5	1.25-2\1-2	150	Second
Gliclazide	323.411	2.6	N\A	2	4	80\2	N\A	
Glipizide	445.538	1.91	5.9	3	6	2.5-40\1-2	75	
Glibornurinde	276.735	N\A	N\A	3	4	N\A	N\A	
Gliquidone	527.636	4.5	N\A	2	6	N\A	N\A	
Glisoxepide	449.526	N\A	N\A	3	7	N\A	N\A	
Glyclopyramide	303.761	N\A	N\A	2	4	N\A	N\A	
Glymidine	309.34	1.27	6.92	1	7	N\A	N\A	
Glimiiride	490.619	3.9	N\A	3	5	1-8\1	350	Third

*N\A: Not Available

Sulfonylurea recent researches

In 2009, four analogs of glibenclamide (glyburide) have shown anti-hyperglycemic activity. These Glyburide derivatives' general structure is shown in fig (3). Glyburide derivatives' substitutes R& R_1 are shown in Table 2. According to this experiment and after evaluating these compounds using experimental animal model, compounds 1 & 3 exhibit good activity as anti-hyperglycemic agents, and compounds 2 to 6 exhibited comparable activity to standard glibenclamide.[13]

Table 2: Glyburide derivatives' R, R_1 substitutes

Compound number	R	R_1
1		
2		$-CH_3$
3		
4		
5		$-CH_3$
6	$-CH_2Cl$	$-CH_3$

Another research has proven that two of N-(4-phenylthiazol-2-yl) benzenesulfonamides derivatives have also anti-diabetic activity. The general structure is shown in fig 4. This activity is exhibited when R is MeO and X is either H or 2,5-dichloro. [15]

Sulfonylurea Structure-Activity Relationship

Authors' perspective:

In 1981, researchers explained that sulfonylurea moiety is not the only one responsible for this group efficacy (Ribes G *et al.,* 1981). They have studies a non-sulphonyl urea acyl-amino-alcyl benzoic acid derivative (HB699) presented in Fig 5. Researchers found that this compound increases insulin secretion when it was injected in rat islets. As a result, it has hypoglycemic activity. However, its potency is three times less than Tolbutamide. [16]

In 1986, Researchers confirmed the previous study that another moiety same as sulfonylurea moiety is responsible for hypoglycemic activity especially in second generation of

sulfonylurea. They found that the non-sulfonylurea moiety of gliquidone derivative (UL-DF 9) also has hypoglycemic activity. This compound structure presented in Fig 6. [17]

These theories explain the superior potency the second and probably the third generation have over the first one. It is estimated that the 2nd generation potency is 100 fold of first generations. [18] This leads to an inquiry. In other words, could be that the more complex sulfonylurea structure becomes, the more their potency increases?! As can be inferred from the chemical structures of sulfonylurea derivates, being R_1 & R_2 small alkyl moieties are probably behind why Tolbutamide is the lowest effective and affinitive to kir6.2\SUR$_1$ compared with other compounds. [14] Tolazamide is more effective with longer efficacy duration than the previous compound. [19] Perhabs this is because of containing hetero alkyl cycle moiety in R_2 makes. On the other hand, Tolazamide is less potent than chlorpropamide which has -Cl in R_1 instead of $-CH_3$ moiety and linear alkyl moiety in R_2. Furthermore, does increase LogP of sulfonylurea compounds and their hydrogen bond acceptors count enhance their efficacy or has an influence on the drug dosage? Table 2 shows the chemical properties of these compounds.

Comparing Tolbutamide, Gliclazide, Glyburide and Glimipiride which respectively their Log P are 2.3, 2.6, 4.9 and 3.5, Hydrogen Bond acceptors count are 3,4,5,5. Glimepiride is the most potent among sulfonylurea derivatives so far. [20] This high lipophilic compound has a great binding with plasma protein. It is very potent and fully absorbed after a dose of 1-4mg a day. It has long efficacy duration though it is half life is only 4 hours. On the other hand, Gliclazide is a potent drug with a dosage of 80mg a day, while Tolbutamide dosage 500-3000 mg\ 2-3 a day with relative potency of 1, and it is not potent enough like the other two 2nd and 3rd generation members that are in Type II diabetes treatment. Glyburide somehow is close to Glimipiride characteristics but probably with its Log P higher than 4.5 has only one active site to interact with. Glimepiride and Gliquidone, their Log P are 3.9 and 4.5 respectively, are also agonists for Peroximose Proliferation Activated Receptor gamma (PPAR γ). Other sulfonylurea compounds; however, still need more investigation and studies for their physical and chemical properties and potency as well.

Sulfonylurea pharmacodynamics based classification

Sulfonylureas have different mechanisms compared with other available oral diabetic medication to decrease glucose blood levels in TYIID patients. [19,21]

These compounds are considered the second preferred line for treatment of Type II diabetes after Metformin.[1] Its mechanism of action is to increase insulin secretion from pancreatic beta cells. [19, 21] Therefore, They are considered inactive for dysfunctional pancreas.[4] Their main active site is ATP sensitive potassium ion channels; Kir 6.2\SUR1; Potassium Inward Rectifier ion channel 6.2\ Sulfonylurea receptor 1. [1] Due to the different isoforms of Kir (Kir $_{6.1}$, Kir $_{6.2\ a\&b}$) with different isoforms of SUR (SUR $_1$,SUR $_2$, SUR$_3$) in other organs than pancreas, it is time to substitute this group old classification with sulfonylurea Kir6.2\SUR1 high and low affinity sub-groups, as less affinity to pancreatic Kir6.2\SUR1 is responsible for cardiovascular adverse effect of a number of sulfonylurea members. [22] Latest Research this year came up with Protein Data Bank ID (PDB) for Kir 6.2\SUR1 receptor combined with Glibenclamide; 6BAA. This structure is the first of its kind in this field, as no 3D structure was presented previously on PDB.com for researchers in medicinal chemistry who have been using Molecular Modelling in developing new compounds as drugs. [23] Glimipiride and gliclazide are considered safer than other sulfonylurea compounds as they respectively cause the least cardiovascular issues. This can be somehow explained by these compounds' structures by noticing R_1, R_2 for each of glimepiride and gliclazide. [24] Nevertheless, this property does not avoid the sudden hypoglycemia the patient might experience by taking sulfonylurea in his medications as anti-hyperglycemic agents. [25]

Pharmacokinetics

Although other pharmacokinetic properties differ from compound to another, Sulfonylurea absorption rates are similar to one another. They are well absorbed from gastrointestinal. [26] Their binding protein percentages are great. They are over 90%. Many sulfonylureas are metabolized in the liver and excreted in a great percentage by the kidneys. Their metabolism is Hepatic by Cytochrome enzymes. They are eliminated, changed, and unchanged compounds. Duration of effect varies from a compound to another, and it depends on the pharmaceutical form the drug is inserted in. It is, for example, between 10-24 h for gliclazide and 3-6 h for chlorpropamide. Half-life is also different. It is longer for chlorpropamide; 36 h, than Glimepiride; 5h, Table 3. [27]

The same case applies for their elimination half-life time. [26] But, in general, their half-life times are short, that is why it is recommended to take these compounds twice a day. [28] Some, but not all, sulfonylureas have active metabolites that may depend upon renal function for their elimination. Table 2 presents sulfonylureas pharmacokinetics.

Table 3: pharmacokinetics characteristics for approved compounds [9,29]

Compound Name	Protein binding	metabolism	metabolites	Metabolite activity*	elimination	Half life (h)	Duration of action (h)
Tolazamide	N\A	Hepatic	5	0-70%	urine	7	4-6
Tolbutamide	95%	Hepatic	2	Mild to inactive	75-85% Urine	4-25	6-12
Glymidine	90%	N\A	N\A	N\A	N\A	4	N\A
Glipizide	98%	Hepatic	2	10-33%	inactive	3-5	IR 1-3 ER:6-12
Chlorpropamide	highly	Hepatic	4	inactive	urine	36	3-6
Gliclazide	94%	Hepatic	6	N\A	60-70%urine	6-15	10-24
Glyburide	99%	N\A	2	Weakly active	50%urine	10 For micronized :2-4	20-24
Glimipiride	99.5%	Hepatic	2	0-33%	N\A	5-9	2-3

N\A: Not Available

***: % of parent compound activity**

Side and Adverse effects

Although sulfonylurea have been in use for more than half decade, It has been known that Hyperglycemic and weight gain are the two most common adverse effects TYIID patient might face during treatment with sulfonylurea agents. [30-31] It is recognized that the possibility of hypoglycemic incidences increases when sulfonylurea is taken in combination with other anti-hyperglycemic agents. [32] This incidence may also happen when the sulfonylurea agent has long effect duration. [33] Weight gain may less occur than hypoglycemic incidences, yet it is not desirable by TYIID patient who is already facing problems with their high weights. Another barrier in maintaining a long term glycaemic control with sulfonylureas is weight gain, which is estimated to be between 2 and 5 kg, depending on the patient's characteristics and effort. [29]

Digestive disturbance is also common with sulfonylurea therapy like any other oral anti-hyperglycemic agents. It is described in abdominal pain, nausea, and diarrhea. [34,35] what decreased sulfonylurea first generation popularity was their association with hepatotoxicity; another adverse effect of sulfonylurea compounds.[36] However, such effect is rare with other

sulfonylurea generations. Cross allergic reactivity is also a possible adverse effect of sulfonylurea. Patients who are allergic to sulfa drugs are 17% possible to experience such allergy. [37] A disulfiram-reaction and cardiovascular increased mortality are another possible adverse effects for using sulfonylurea agents for a long term. [39]

Insulin is the safest treatment for TYIID in pregnant women. Yet, Glyburide has been examined to be used in this case according to Food and Drug Administration (FDA) sulfonylurea pregnancy category: C. [40] On the other hand, studies have shown that Glyburide does not pass the umbilical cord in significant amounts, which, in returns, supports that neonatal hypoglycemia is not one of Glyburide adverse effects during pregnancy. [40,41] However, more clinical studies must be done before deciding how safe sulfonyl urea usage in pregnancy is.

Contraindications

Sulfonylureas should be administered with caution in patients with either renal or hepatic insufficiency. All sulfonylureas have a low clearance. [9] Cardiovascular diseases are considered a massive challenge facing sulfonylurea usage in TYIID treatment as they increase the mortality among these patients. [42, 43] Contraindications for these drug usage include type 1 DM, pregnancy, lactation, significant hepatic and renal insufficiency. [9]

Sulfonylurea in Drug Stocks

Sulfonyl urea is presented to the market under many trade names solely or in combination with other oral anti-hyperglycemic agents such as Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®; Glucotrol® XL) Glyburide (Diabeta®; Glynase®) Tolazamide (Tolinase®) Tolbutamide (Orinase®) Glipizide & Metformin (Metaglip™) Glyburide & Metformin (Glucovance®) Pioglitazone & Glimepiride (Duetact™) Rosiglitazone & Glimepiride (Avandaryl®) More than 25% of noninsulin antidiabetic drug prescriptions were for sulfonylureas, divided beinto three second-generation sulfonylureas (glipizide, glimepiride, and glyburide).It is also indicated that 22.1% of the metformin market share was concomitant with the use of sulfonylureas. On the other hand, sulfonylurea share in oral antihyperglycemic drugs market share decreased 9.6 % between 2003- 2012 due to the rise of new approved anti-diabetic agents during the last decade which quickly gained significant market share. [44]

CONCLUSION

We shaded light on the chemical differences among sulfonylurea compounds, their pharmacodynamic and pharmacokinetic characteristics in addition to the adverse effects that caused each compound to be withdrawn or continued in clinical use for Type II diabetes treatment. On the other hand, we recommend that much more studies to be done on Sulfonylurea structure activity relationship in a try to get valid answers to our debate that lead to new sulfonylurea agents with reduced adverse effects which had affected or rather limited sulfonylurea reputation as effective anti-diabetic agents. Hence, identifying the crystal structure of Kir6.2\SUR1 combined with one of sulfonylurea compounds in PDB assists researchers in medicinal chemistry who use Molecular Modelling in developing new sulfonylurea agents.

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Figures

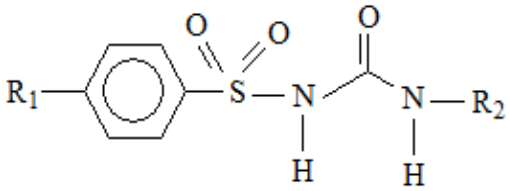
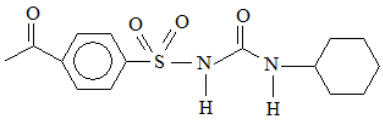
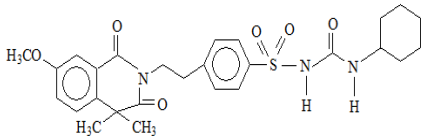
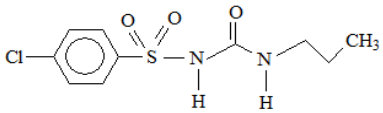
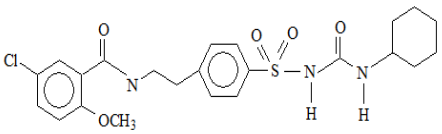
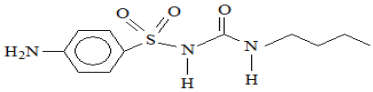
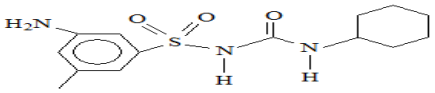
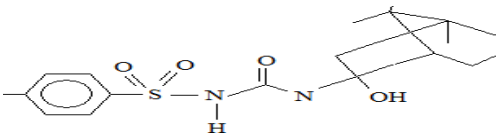
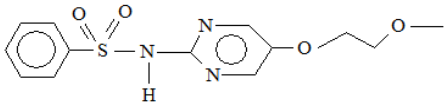
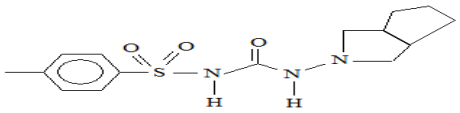
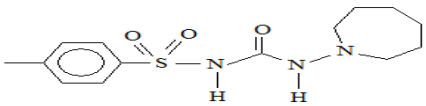
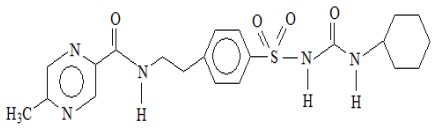
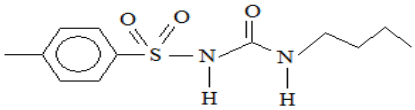


Fig 1: Sulfonylurea general structure

Acetohexamide 	 Gliquidone
Chlorpropamide 	 Glyburide
Carbutamide 	Metahexamide 
 Glibornuride	Glymidine 
Gliclazide 	Tolazamide 
Glipizide 	Tolbutamide 

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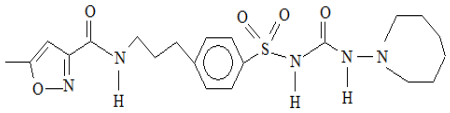
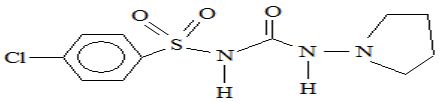
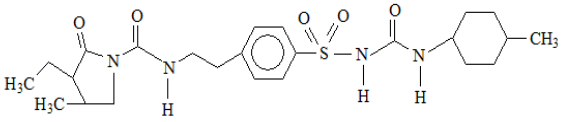
	
Glimepiride	
	

Fig 2: Sulfonylurea compounds' structures

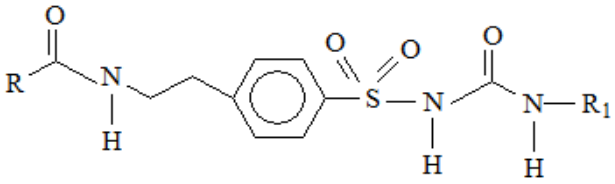


Fig 3: Glyburide derivatives' general structure

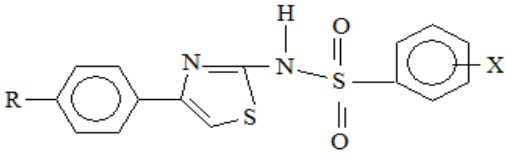


Fig 4: general structure of N-(4-phenyl thiazole-2-yl) benzenesulfonamides derivatives

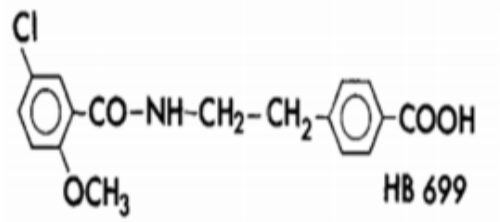


Fig 5: a mom-sulphonyl urea acyl-amino-alkyl benzoic acid derivative (HB 699) structure

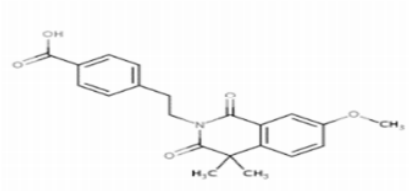


Fig 6: the non-sulfonylurea moiety of gliquidone derivative (UL-DF 9) structure