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Sulfonamides : Historical Discovery Development (Structure-Activity Relationship Notes)

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Abstract

Sulfonamide group is a magic group introduced as the main core for different bio-activities in drug industry. According to its substitutes, literature divides sulfonamide derivatives to antibacterial sulfonamides and non-anti-bacterial sulfonamides. As Data was collected from different sources such as Drug Bank.com and Pubchem.com databases and then was analyzed, we found that these compounds are different in their pharmacokinetics and pharmacodynamics; in addition to their sulfa cross allergy property. We presented these differences from these compounds changes in their chemical structure, in a way to build a solid base that can be depended on for developing new drugs from these compounds that interact with different receptors.

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Introduction:

Sulfonamide derivatives medical groups' discovery can be more similar to a string of distinguished pearls. They have in common the same main core but they differ in their bioactivities;[1] [2]The common core structure of sulfonamide is illustrated in Fig 1. Literature used to divide sulfonamides into anti -bacterial sulfonamides; with an aromatic amine, and non-anti-bacterial sulfonamides; without an aromatic amine.[3] The last includes agents work as anti-inflammatory, anti-hyperglycemia, diuretics, serotonin antagonists, or other different pharmacology. [2] [3] As we assume in this paper this activity depends on the substitutes that the compound chemical structure has in addition to sulfonamide group. We tried here to collect sulfonamide drugs properties and chemical structures to compare between them from structure differences that reflect on the activities they have. In other words we tried to set Structure-Activity-Relationship (SAR) from these chemical structures for sulfonamide core. This helps the researchers more in case they need a reference for these compounds collected in one paper.

Anti-Bacterial Sulfonamides:

Sulfonamide was firstly noted as anti-bacterial in 1900's by Gerhard Domagk; a Nobel Prize winner in 1939. In his attempt to save his daughter from streptococci killing infection, he observed that prontosil; a sulfonamide dye, is able to selectively restrain the infectious bacteria cells. In 1936, Ernest Fourneau found out prontosil pathway in human body. He discovered that this dye was a pro-drug. It, actually changes in human body to sulfanilamide which is the anti-bacterial active agent.

This invention triggered the discoveries of other anti-bacterial members derived from this chemical group such as sulfapyridine in 1938 against pneumonia, and sulfacetamide in 1941 against urinary tract infections, and succinoylsulfathiazole in 1942 against gastrointestinal tract infections. Sulfathiazole was commonly used during World War II to cure soldier wounds' infections. On the contrary, sulfanilamide was not very used due to its greater human toxicity. Later on, sulfisoxaide, sulfamethoxazole, sulfacetamide, mafenide and sulfadiazine silver were discovered, and those four agents are the sulfonamide anti-bacterial agents have been in the clinical use so far.

Sulfonamide anti-bacterial medications; also called sulfa drugs, are competitive inhibitors of p- amino benzoic acid in the folic acid metabolism cycle in the organisms . [4] [5] They have a common core structure shown in Fig 2.

They can be classified as Oral absorbable, oral non-absorbable, and topical agents.[4] Oral absorbable agents are also divided into short acting agents such as sulfisoxaide, medium acting agents such as sulfamethoxazole and long acting agents such as sulfasalazine.

Oral non absorbable agent group includes only sulfasalazine, while topical agents have sulfacetamide, mafanide, and silver sulfadiazine. Chemical structures of these groups are shown in Fig 3, and their properties are shown in Table 1. Sulfonamides that do not contain this aromatic amine group undergo different metabolic pathways.[6]

Non Anti-Bacterial Sulfonamide:

Anti-Hyperglycemic Agents:

This group of drugs is commonly used in type 2 diabetes treatment.[7] These drugs' history goes back to 1937, when Ruiz made experiments on sulfa drugs.[8] [9] [10] Later, in 1942, Janbon confirmed this efficacy when anti-bacteria sulfonamide;

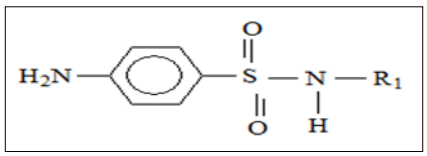


Fig 1: Sulfonamide common core structure

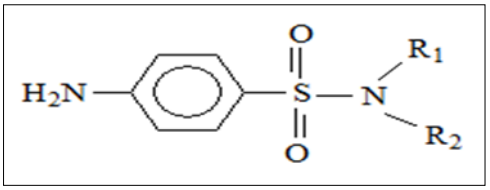


Fig 2: Anti bacterial Sulfonamide 's common core structure

p-amino-sulfonamide-isopropylthiodiazole, caused such an efficacy as side effect in patients treated from typhoid. [11]

Studies on sulfonamide bioactivities expanded when Laboratories proved that sulfa drugs stimulated beta cell release of insulin. [1] In 1950s, carbutamide; 1-butyl-3-sulfonylurea, was the first sulfonylurea compound presented in the clinical use for diabetes therapy , but not for too long as it had adverse effects on bone marrow.[3]

In 1956, Germany introduced tolbutamide; sulfa drugs derivative, as the first sulfonylurea compound to be in clinical use for diabetes treatment. Other first generation sulfonylurea compounds; 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; after more than a decade of their usage in Europe. [12] Furthermore, glimipiride, the most potent sulfonylurea compound, was not commercially introduced till 1995 in the US drug market. [13]

The mechanism of anti-hyperglycemic agents action is the increase of insulin hormone secretion from pancreatic beta cells.[14] [15] [16] Therefore, they are considered inactive for dysfunctional pancreas. [17] Their main active site is in ATP sensitive potassium ion channels; Kir 6.2\SUR1; Potassium Inward Rectifier ion channel 6.2\ Sulfonylurea Receptor 1.

The common core structure of these compounds is presented in Fig 4. From this structure, it can be found that these sulfonylurea compounds are derived from sulfonamide (Fig1) by replacing R_1 with (-CO-NHR$_2$) and R_2 with H, NH_2 with R_3. R_1,R_2,R_3 in sulfonylurea structure which are responsible for the different properties sulfonylurea compounds have. Fig 5 shows sulfonylurea family members and Table 2 shows their properties.

It is worth mentioning that not all sulfonylurea derivatives are anti-hyperglycemic agents. Most of them are herbicides.[18] To eliminate the confusion about this point, it is important to present the common core structure of these sulfonylurea herbicides;[6] (Fig 6), which shows the difference between them and anti-hyperglycemic agents derived from sulfonylurea.

Diuretics:

We all know that diuretics play an effective role in hypertension treatment.[19] There are many pharmaceutical combinations between them and anti-hypertension agents.[20] In general, diuretics such as carbonic anhydrase inhibitors, thiazides and loop diuretics are sulfonamide compounds. The chemical structures of these sub-group members are shown in Fig 7. Loop diuretics are considered safer and high ceiling diuretics. Their efficacy has linear relationship with their doses, to the contrary of thiazides which are low-ceiling diuretics.[21] [22] These properties can be attributed to the reason that the loop diuretics are sulfonamide derivatives not thiazide ones.

Fig 8 shows the common core structure of thiazide diuretics, and Fig 9 presents thiazide family members. Loop diuretic common core structure is presented in Fig 10; where X can be N or C, while Fig 11 presents different members of it. Table 3 presents diuretic compounds' properties.

Thiazide acts at the proximal part of the distal tubule. They interfere with Sodium transfers which increases excretion and urine volume. This results in a reduction of blood volume.[23] These diuretics are well absorbed after oral administration, well distributed and undergo a hepatic metabolism. Since their effect target tissues are the kidney , renal failure decreases their efficacy. Thiazides must be taken in awareness with beta-blockers. Together are considered a high risk to cause diabetes in people with impaired glucose tolerance, features of the metabolic syndrome, or obesity.

Serotonin Antagonists:

Many sulfonamide compounds are 5-HT3 receptor antagonists. As a consequence, they work as anti depressants such as Naratriptan and Sumatriptan. [23] Fig 12 shows chemical structures of these compounds, and Table 4 presents their properties.

Anti– Inflammatory Agents:

Celecoxib, rofecoxib, and valdecoxib are sulfonamide derivative work as anti-inflammatory agents.[24] Their mechanism of action is selectively inhibiting Cyclo-Oxygenase-2 Enzyme

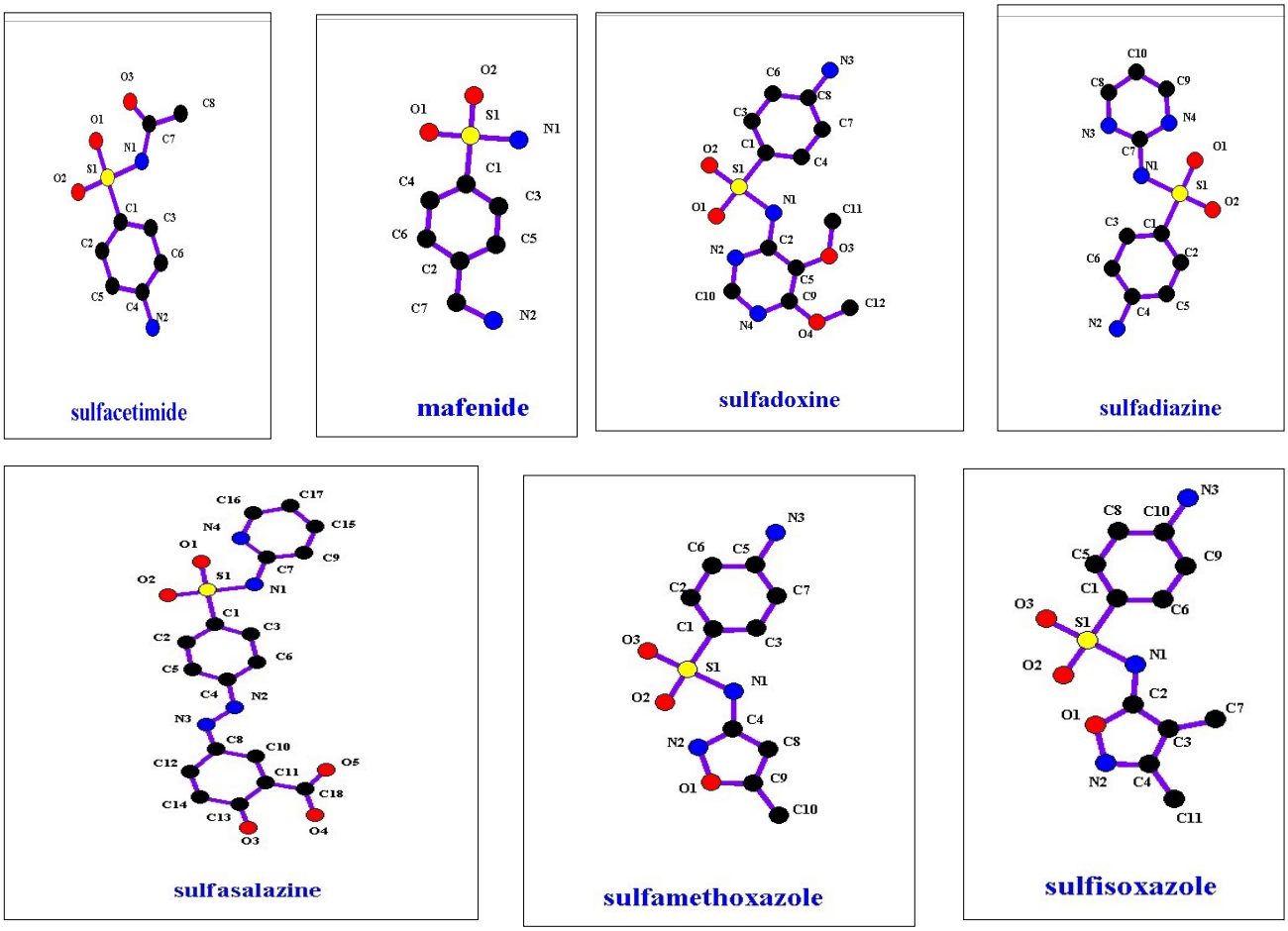


Fig 3: Anti bacterial Sulfonamide members' structures

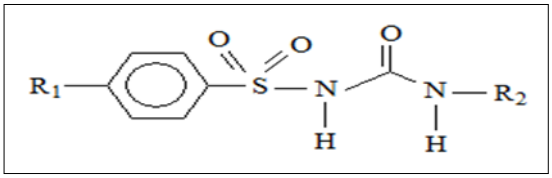


Fig 4: Sulfonylurea general structure

Table 1: anti-bacterial sulfonamide properties.[1]

Compound Name	Log P	Molecular Weight	$T_{1/2}$
Sulfisoxazole	1.01	267.303	6
Sulfamethoxazole	0.89	253.276	10
Sulfadoxine	0.7	310.328	N\A
Sulfasalazine	3.8	398.393	5- 10
Sulfacetamide	-0.96	214.239	7-12.8
Mafenide	N\A	186.229	N\A
Silver Sulfadiazine	N\A	357.136	N\A

Table 2: Anti hyperglycemic sulfonylurea properties [6]

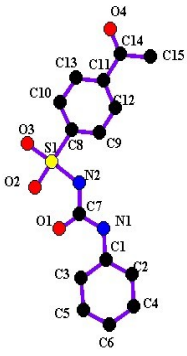
Compound Name	pK_a	Log P	Molecular Weight	$T_{1\2}$
Tolbutamide	5.16	2.3	270.347	7
Tolazamide	3.6	2.69	311.4	7
Acetohexamide	6.6	2.3	324.395	N\A
Carbutamide	N\A	1.01	271.335	N\A
Chlorpropamide	5.13	2.2	276.735	36
Glycyclamide	N\A	N\A	296.119	N\A
Metahexamide	3	N\A	311.4	N\A
Glyburide	N\A	4.9	494.003	2-4
Gliclazide	N\A	2.6	323.411	6-15
Glipizide	5.9	1.91	445.538	3-5
Glibornurinde	N\A	N\A	276.735	N\A
Gliquidone	N\A	4.5	527.636	N\A
Glisoxepide	N\A	N\A	449.526	N\A
Glyclopyramide	N\A	N\A	303.761	N\A
Glymidine	6.92	1.27	309.34	4
Glimiiride	N\A	3.9	490.619	5

Table 4: Sulfonamide anti depressants' properties [6]

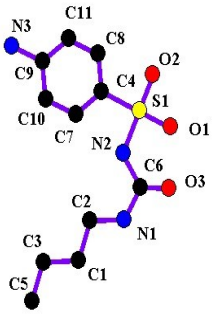
Compound Name	Log P	Molecular Weight g\mole	$T_{1\2}$ (h)
Sumatriptan	1.6	335.466	5-8
Naratriptan	0.93	295.401	2.5

Table 3: Diuretics' properties [6]

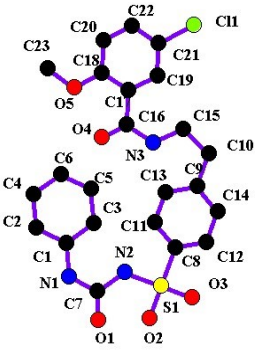
Compound Name	pKa	Log P	Molecular Weight g\mol	$T_{1\2}$ (h)
Acetzolamide	7.2	-0.45	222.237	9
Brinzolamide	N\A	-1.8	383.496	111 day
Dichlorophinamide	7.4	0.2	305.144	N\A
Dorzolamide	N\A	-1	324.428	4 months
Methazolamide	7.3	0.13	236.264	14 h
Sulthiame	N\A	N\A	290.352	N\A
Metolazone	9.72	2.5	365.832	14 h
Bendroflumethiazide	8.5	1.19	421.409	8.5
Chlorothiazide	6.85	-0.24	295.712	2 h
Chlortalidone	N\A	0.85	338.762	40 h
Clopamide	N\A	N\A	345.842	N\A
Diazoxide	8.74	1.2	230.666	28 h
Hydrochlorthiazide	7.9	-0.07	297.728	14.8
Hydroflumethiazide	8.9	0.36	331.284	27 h
Indapamide	8.8	2.2	365.832	14
Xipamide	N\A	N\A	354.805	N\A
methyclothiazide	9.4	1.42	360.224	N\A
Bumetanide	N\A	2.6	364.416	60-90 min
Furosemide	N\A	2.03	330.739	1.5
Piretanide	N\A	3.92	362.4	N\A
torasemide	N\A	2.3	348.421	3.5



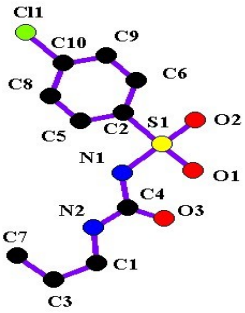
acetohexamide



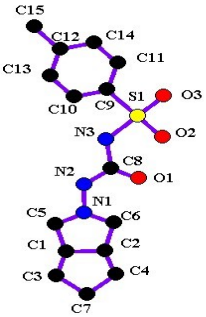
carbutamide



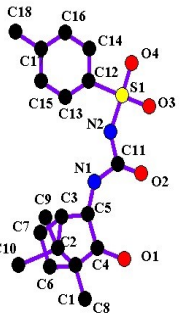
glibenclamide



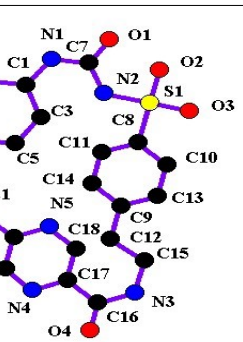
chlorpropamide



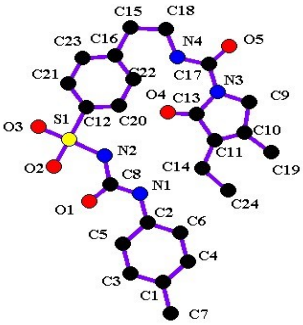
gliclazide1



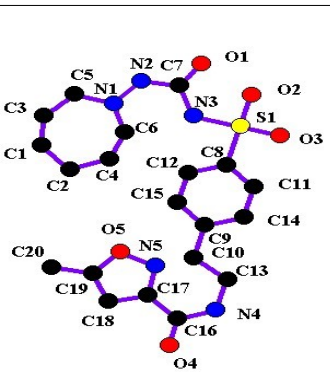
glibornuride



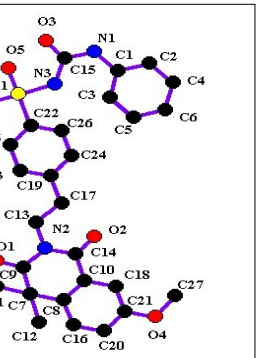
glipizide



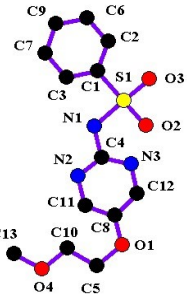
glimipiride



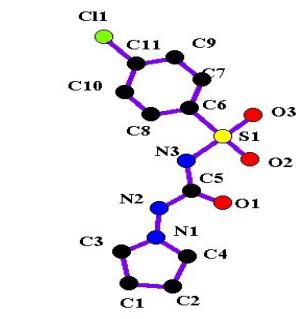
glisoxepide



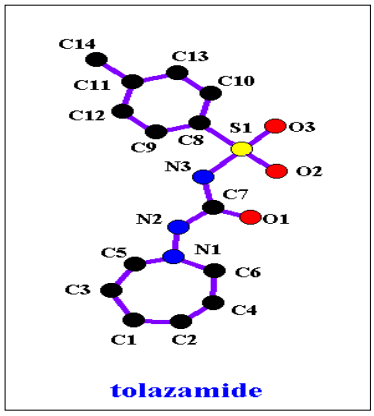
gliquidone

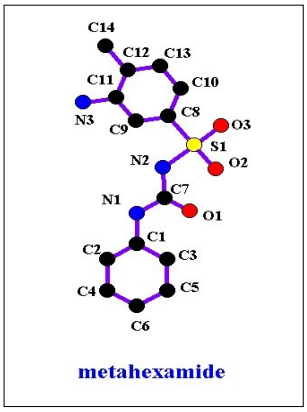


glymidine



glycopyramide





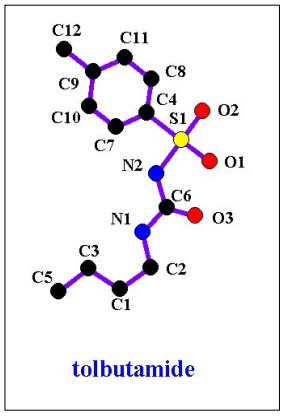


Fig 5: Sulfonylurea anti-hyperglycemic agents' structures

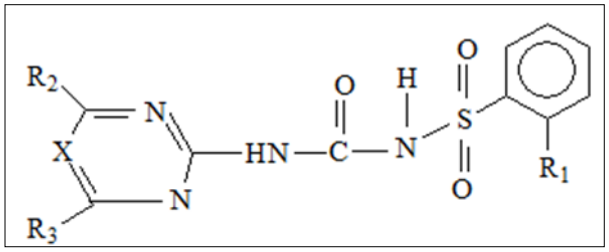


Fig 6:sulfonylurea herbicides' structures

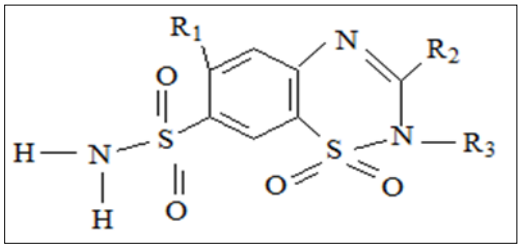
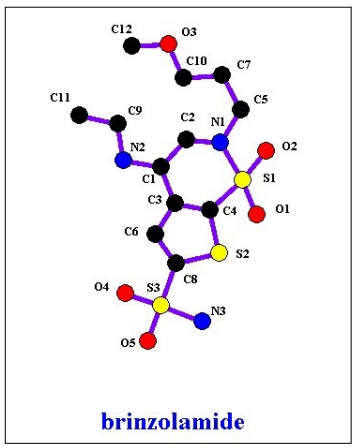
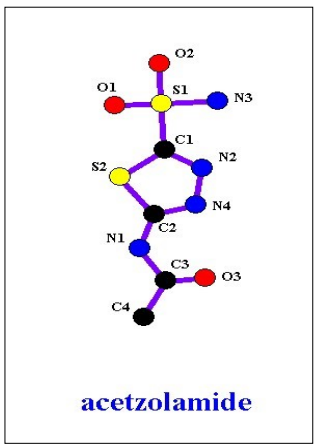
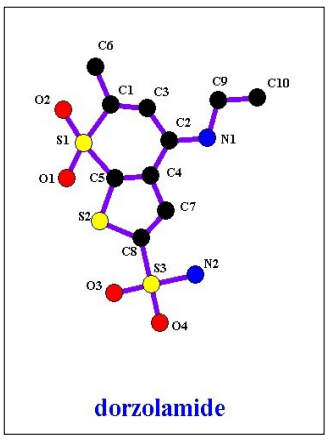
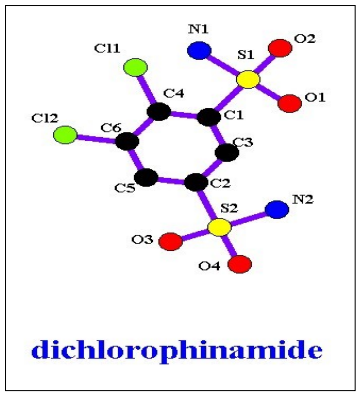


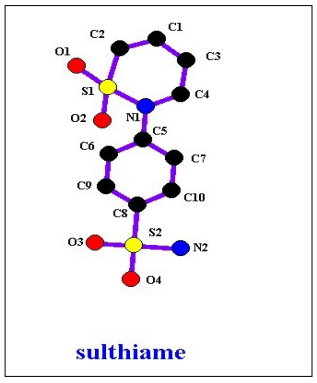
Fig 8: Thiazide diurectics' general structure











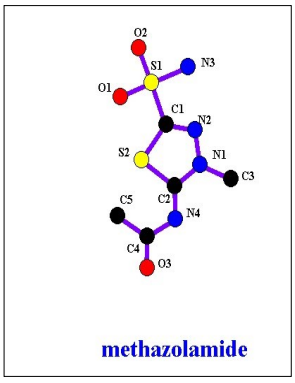
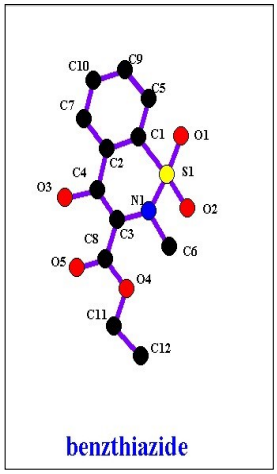
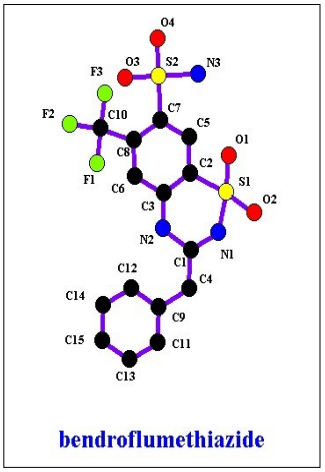
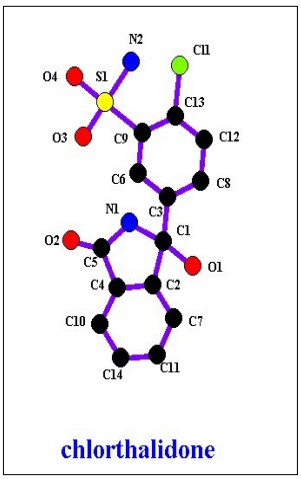
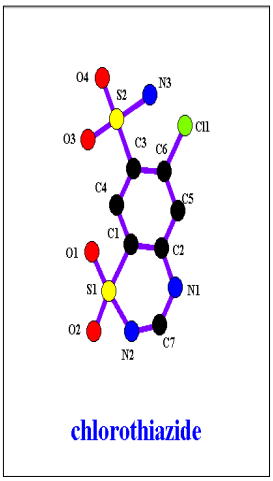


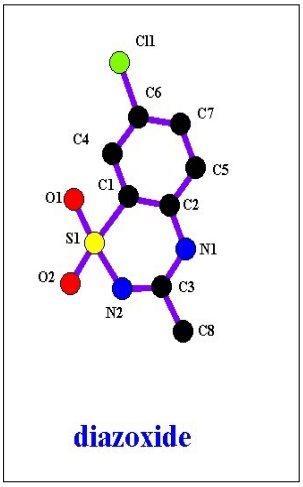
Fig 7: carbonic anhydrase inhibitors' structures

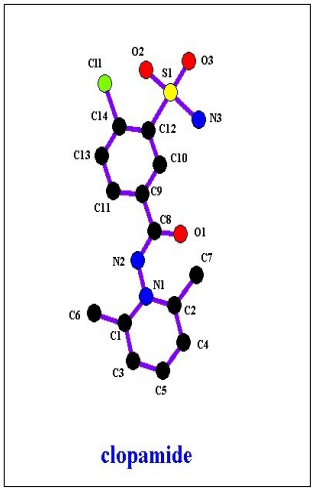


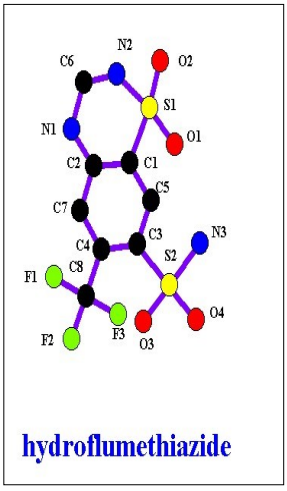


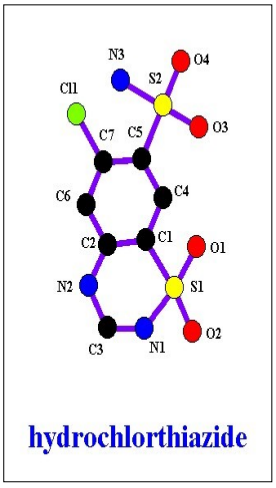


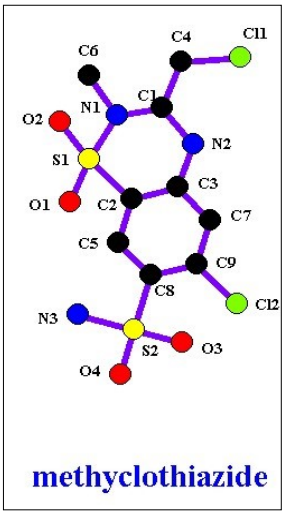


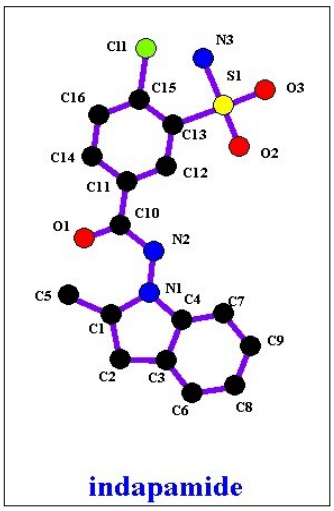


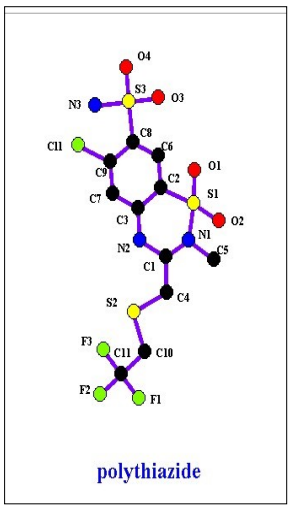


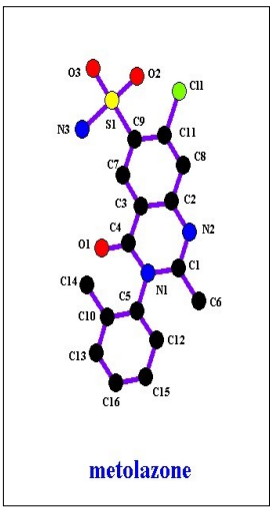












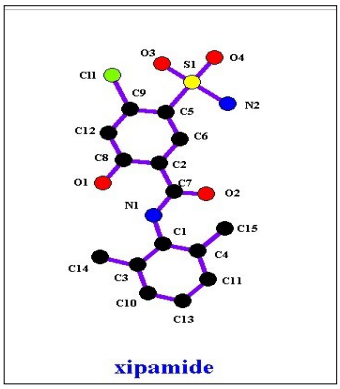


Fig 9: Thiazides structures

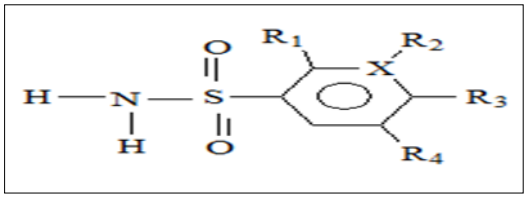


Fig 10: Loop diuretics' general structure

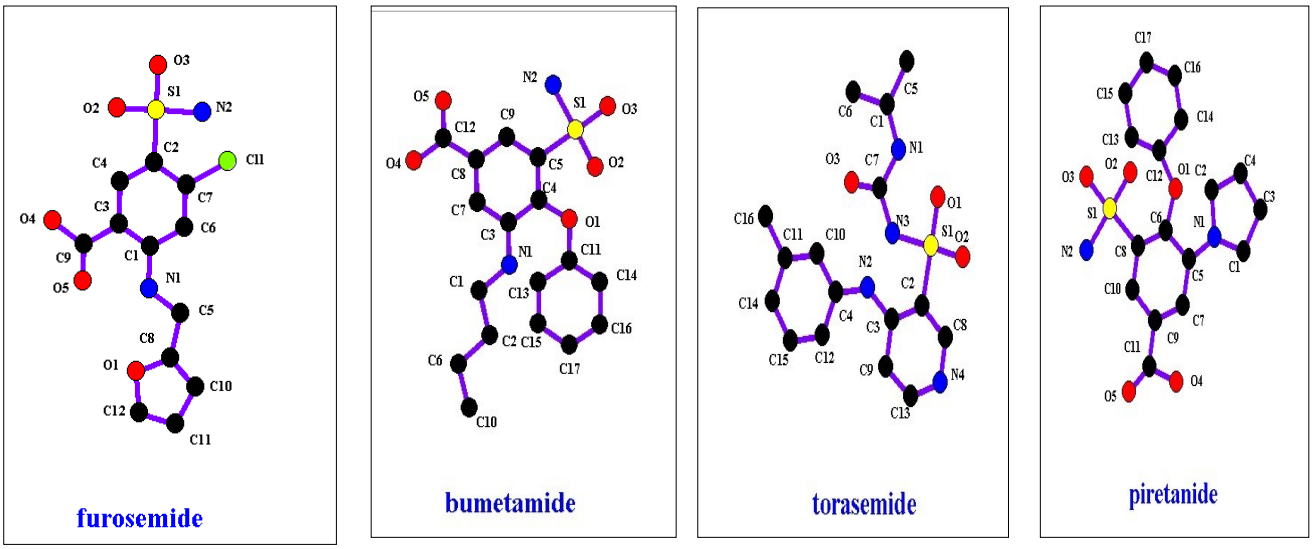


Fig 11: loop diuretics' structures

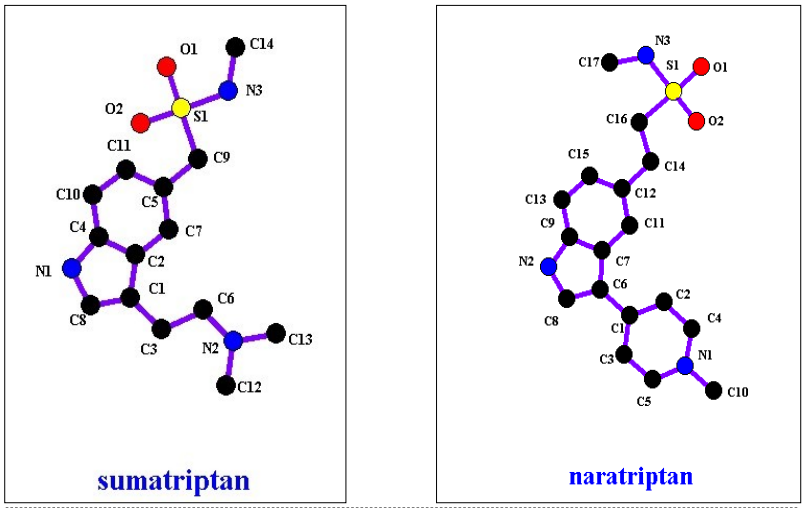


Fig 12: Sulfonamide anti depressants' structures

(COX-2 enzymes).[25] This prevents prostaglandins and other inflammatory substrate production. Fig 13 illustrates their chemical structures. Table 5 presents their properties.

Other Pharmacological Sulfonamide Compounds:

These include protease inhibitors with activity against Human Immunodeficiency Virus Type 1 (HIV-1) such as amprenavir and fosamprenavir,[26],[27] anti convulsant agent used in the treatment of epilepsy and migraine such as topiramate,[28] anti hypertension as sotalol,[29] anti-inflammatory and immunosuppressive agent with anti bacterial and antibiotic properties such as dapsone, anti-arrhythmia agent as Ibutilide, a uricosuric and renal tubular blocking agent; Probencid which is used to treat chronic gouty arthritis, and anti seizure such as zonisamide. These compound chemical structures are shown in Fig 14, and their properties are shown in Table 6.

Structure Activity Relationship Notes:

Comparing the common core structures between the different groups of sulfonamide based on their bioactivity, we conclude to:

Anti-Bacterial agents: NH_2 bounded to aromatic group is free with no bounded moieties. while R_1 connected to NH_2 in sulfonamide group could be H or any heterocyclic group.

Anti-hyperglycemic agents: Substituting aromatic NH_2 with R1 (this could be NH_2 or Alkyl moiety). It also has sulfonylurea moiety instead of sulfonamide group where R_2 connected to urea moiety could be Alkyl, Aromatic group, or heterocyclic group.

Herbicides: They also have sulfonylurea group, but it has R_1 in orto position instead of the aromatic NH_2 which was in the para position. R_2 moiety connected to sulfonylurea group is aromatic heterocyclic group.

When the sulfonamide group is free of moieties from NH_2 side. While R_1 connected to SO_2 group differs between the pharmacologic groups as follows:

Carbonic anhydrase inhibitors: R_1 is aromatic hetero cyclic group.

Thiazides: R_1 is aromatic cycle, where Cl or F is in orto position. In para position, heterocyclic group or a moiety that has SO_2 could bound.

Loop diuretics: R_1 is aromatic cycle with groups in orto or para positions.

Serotonin ant-agonists: R_1 is alkyl moiety connected to hetero cycle which might be aromatic or non aromatic.

Anti-inflammatory agents: R_1 is Aryl group where in para position there is heterocyclic group.

Sulfa Drug Cross-Allergy:

Studies have proved non cross allergic reactivity among sulfa based structure drugs. In fact, allergy

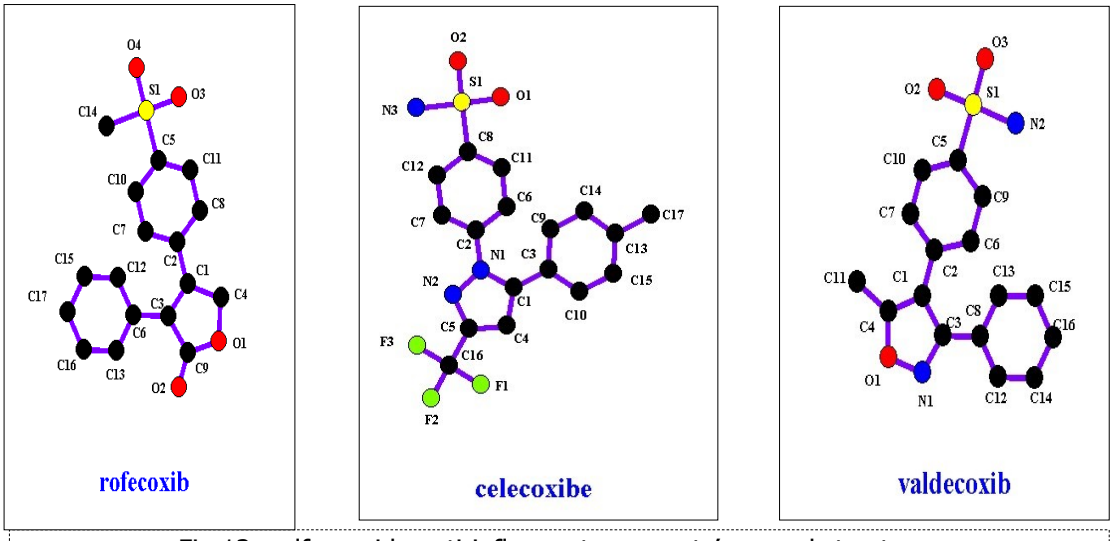


Fig 13: sulfonamide anti-inflammatory agents' general structures

Table 5: sulfonamide anti-inflammatory agents' properties [6]

Compound Name	Log P	Molecular Weight g\mole	$T_{1\2}$ (h)
Celecoxib	3.47	381.373	11
Rofecoxib	1.56	314.355	17
Valdecoxib	2.67	314.359	8-11

Table 6: sulfonamides with different pharmacologies agents' structures [6]

Compound	pKa	Log P	Molecular Weight g\mole	$T_{1\2}$ (h)
Amprenavir	-------	2.2	505.63	7.1-10.6
Fosampre-navir	1.7	2.2	585.609	7.7
Dapsone	2.41	0.97	248.3	28
Ibutilde	--------	4.31	384.579	6
Probencid	3.4	3.21	285.358	6-12
Sotalol	------	0.24	272.363	12
Zonisamide	10.2	0.36	212.223	63
Topiramate	-------	-0.7	339.359	21

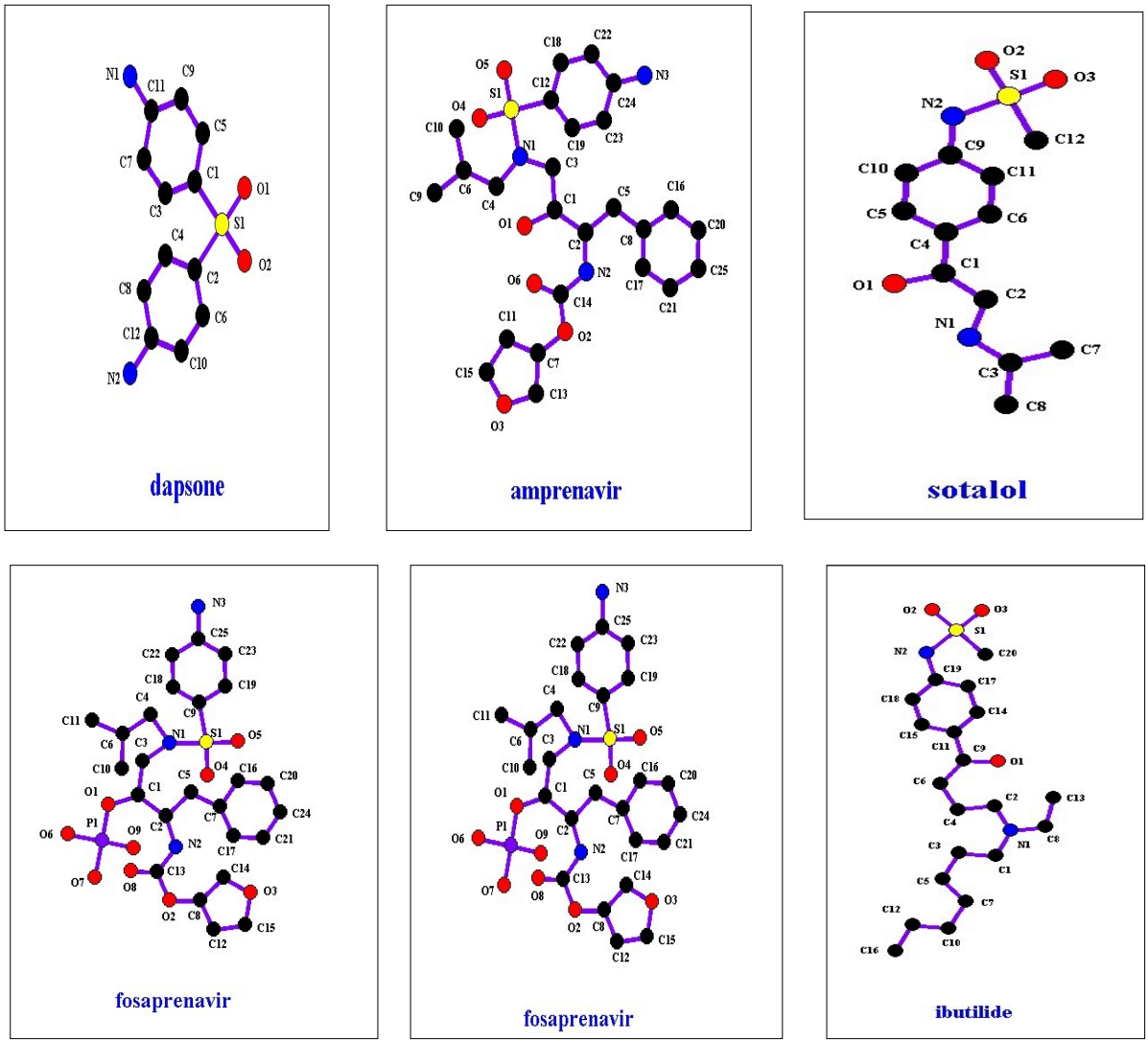


Fig 14: sulfonamides with different pharmacologies agents' structures

incidences toward these medication happen commonly in antibacterial sulfa drugs, but not in the other sulfa based compounds.[30]

However, sulfonamide diuretics are not far from the risk of cross-reactivity of sulfonamide allergy. Patients who are allergic to other sulfonamides showed doubled allergic reactivity toward sulfonamide diuretics. [31]

Conclusion:

This paper has presented a number of compounds that were derived from this unique chemical group with a variety of pharmacological effects that served human health. We consider sulfa drugs are a great discovery. One can develop chemical structure as potential drugs in the future by substituting R moieties or adding halogens or inserting any changes the researcher finds necessary in sulfonamide structure for his drug development. One can also have molecular modeling for one compound from different sub-activity groups to find out if they have any effect on the other compounds receptors in a way to develop new agents from the same chemical group.

Reference:

1. Ayub, Z.; Ayub, S.; Shakoor, M., Sulfa allergy: cross-reactivity versus multiple concurrent allergies, American journal of infectious diseases, 2013, 4, p: 148-154.
2. Branowska, D.; Fusiarz, I., Biological activity and

synthesis of sulfonamide derivates: a brief review, Chemik, 2014, 68, 7, 620-628.

3. Schinnar, R., Apter, A.J., Absence of cross reactivity between sulfonamide antibiotics and sulfonamide non-antibiotics, N. ENGL. J. MED., 2003, 1628-1635.
4. Kishore, D.; Pareek A., A short review on sulphonamides, International journal of pharma and bio sciences, 2013, Vol: 4, p: 812-820.
5. Lesch, JE., The first miracle drugs: how sulfa drugs transformed medicine, New York: Oxford University Press, 2007, x, 364p. p.
6. Healy R. Which diuretics are safe and effective for patients with a sulfa allergy?, The Journal of Family Practice, Vol 56, No 6 / June 2007: 488-490.
7. Uzor, Ph.; Patience, O., Oral anti-diabetic agents –review and updates, Bristish journal of medicine and medical research, 2015, Vol 5, p: 134-159.
8. Levine R. Sulfonylureas: Background and development of the field. Diabetes Care 1984; 7 (Suppl 1): 37.
9. Seltzer H. Efficacy and safety of oral hypoglycemic agents. Annual Review of Medicine 1980; 31: 26172.
10. Bastaki S., Review Diabetes mellitus and its treatment, Int J Diabetes & Metabolism (2005) 13:111-134.
11. Celeste C. L. Quianzon, MD and Issam E. Cheikh, MD, History of current non-insulin medications for diabetes mellitus, Journal of Community Hospital Internal Medicine Perspectives 2012, 2: 19081 - http://dx.doi.org/10.3402/ jchimp.v2i3.19081
12. Kleppinger EL, Vivian EM. Pramlintide for the treatment of diabetes mellitus. Ann Pharmacother 2003; 37: 10829.
13. Amaryl [Internet]. Silver Spring, Maryland: U.S. Food and Drug Administration. Available from: http://www.accessdata.fda.gov/scripts/cder/ drugsatfda/index.cfm?fuseactionSearch. DrugDetails [cited 29 February 2012].
14. Aschcroft F.; Proks P., Sulfonylurea stimulation of insulin secretion, Diabestes, 2002, Vol 51, p:368-376.
15. Aschcroft F.; Proks P., Sulfonylurea stimulation of insulin secretion, Diabestes, 2002, Vol 51, p:368-376.
16. Moller D.; Zhou g., Role of Amp- activated protein kinase in mechanism of metformin action, The journal of clinical investigation, 2001, Vol 108, p: 1167-1174
17. Levine R. Sulfonylureas: background development of the field. Diabetes Care 1984; 7 (supplement 1): 3-7.
18. Duggleby, R.; Wang, J., Structure-activity relationships for a new family of sulfonylurea herbicides, Journal of computer-aided molecular design, 2005, vol:9, p: 801-820.
19. Smith, H., S AFR PHARM J, 2014, vol:81, p:18021.
20. Collins, R.; Peto, R.; Hennekens ch: blood pressure, stroke, and coronary heart disease. Part 2: short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. Lancet, 1990, 335, p: 827-838.
21. Ghiadoni, l.; Salvetti, A., Thiazide diuretics in the treatment of hypertension: an update, Journal of American society of nephrology, 2006, Vol:17, p: 26-29.
22. Housten MC, THIAZIDE and thiazide-like diuretics in hypertension, Ann Intern Med;Aug;103(2):303.
23. Janssens, J.; Peters, T., Actions of 5- hydroxytriptamine 1 receptor agonist sumatriptan on intergigestive gastrointestinal motility in man, 1998, Vol: 42, p: 36-41.
24. Bombardier, C.; Laine, I., Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis, N. ENGL. J. MED, 2000, p: 1520-1528.
25. Day, R., Cox-2 inhibitors, Medical journal of Australia, 2000, Vol: 23, p: 30-32.
26. Schooley, R.; Myers, R., A dose- ranging study to evaluate theantiretroviral activity and safety of amprenavir alone and in combination with abacavir in HIV-infected adults with limited antiretroviral experience, Antiviral therapy, 2001, Vol: 6, p: 89-96.
27. Wire M., khaled M., Fasoamprenavir\ ritonavir in

advanced HIV disease (TRIAD):a randomized study of high-dose, dual-boosted or standard dose fosamprenavir\ ritronavir in HIV-1-infected patients with antiretroviral resistance, Journal of antimicrobial chemotherapy, 2009, Vol: 64, p: 398-410.

28. Chaverri J.; Garcia M., Antioxidant activity of topiramate: an antiepileptic agent, neurological sciences, 2012.
29. Woolsey R., Wood A., A mechanism of d- (+)- sotalol effects on heart rate not related to beta- adreniceptor antagonism, British journal of clinical pharmacology, 1990, Vol: 30, p: 195-202.
30. Wulf NR, Matuszewski KA, Sulfonamide cross- reactivity: is there evidence to support broad cross- allergy? Am J Health Syst Pharm. 2013 Sep 1;70 (17):1483-94. DOI: 10.2146/ ajhp 120291.
31. Which diuretics are safe and effective for patients with a sulfa allergy?, Ron Healy, MD, The Journal of Family Practice, Vol 56, No 6 / June 2007: 488-490