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Review Article

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Therapeutic Aspects of Sulfonylureas: A Brief Review

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ABSTRACT

Sulfonylureas are a class of organic compounds used in medicine and agriculture. All pharmacologically active sulfonylureas contain a central S-aryl sulfonylurea structure with a p-substituent on the phenyl ring and various groups terminating the urea N′ end group. Chemically, this functionality can be easily installed by reacting aryl sulfonamides with isocyanates. The current survey focused on some well-established method for preparation of sulphonylurea followed by their pharmacological profile. It is primarily used for the treatment of diabetes mellitus type 2 a pancreatic disorder. Though It also has some extrapancreatic effect like anti-cancer, diuretic, anti-inflammatory, anticonvulsant and neuroprotective agents etc which is discussed in our paper.

Keywords*:* Sulphonylurea, Sulphonation, Antidiabetic, anticancer, anti-inflammatory, neuroprotective.

INTRODUCTION

Sulfonylureas were discovered in 1942 by the chemist Marcel Janbon and co-workers [1]. Sulfonylureas derivative contain a central S-aryl sulfonylurea structure with a p- substituent on the phenyl ring (R1) and various groups terminating the urea at N′ end group (R2). Chemically, this functionality can be easily installed by reacting aryl sulfonamides (R1-C6H4-SO2NH2) with isocyanates (R2-NCO)[2].

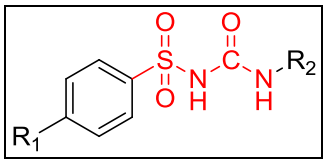
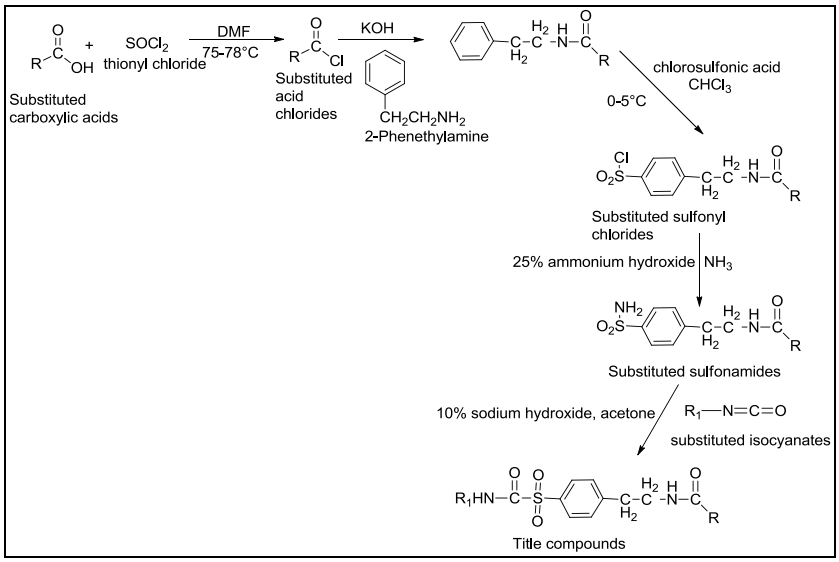


Figure: 1

These compounds also exhibit a wide range of biological activities like antidiabetic, diuretic[3], histamine H3 receptor antagonism[4], thromboxane A2 receptor antagonism[5], antimicrobial, antimalarial[6], antitubercular[7], anticancer or cytotoxic and anti-inflammatory activity.

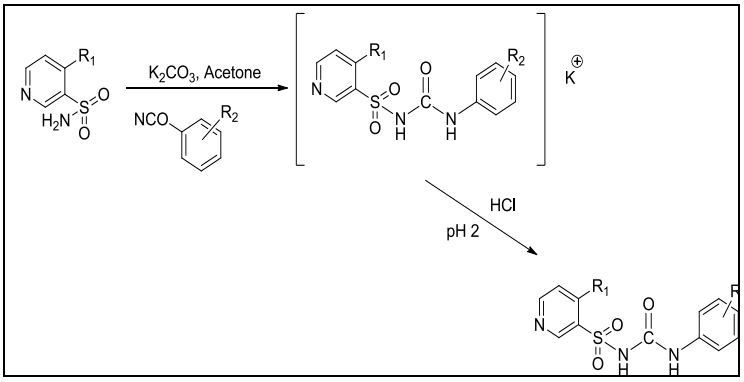
Synthesis of some sulfonylureas derivative

Scheme 1 describes the synthesis of some novel analog of Glibenclamide, a second-generation sulfonylurea. The various substituted carboxylic acids were refluxed with thionyl chloride to give corresponding acid chlorides. The individual acid chlorides were further treated with 2-phenethylamine in presence of base to produce corresponding amides. The corresponding sulfonamide derivatives were prepared by chloro- sulfonation and amidation of respective amides, followed by reaction of sulfonamide derivatives with isocyanates[8].



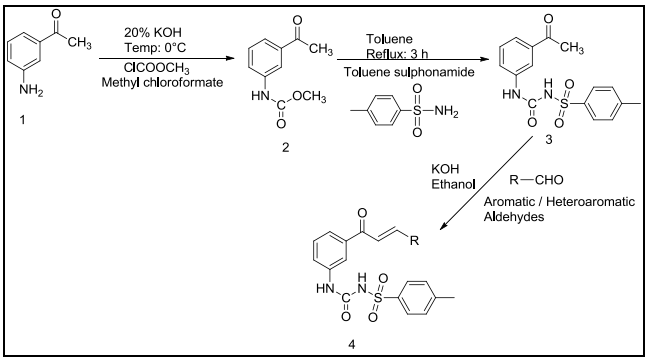
Scheme 1

As per scheme-2 4-substituted N-(phenyl carbamoyl)pyridine-3-sulfonamides were obtained by treatment of primary sulfonamides with the appropriate aryl isocyanates in dry acetone, at room temperature in the presence of anhydrous potassium carbonate[9].



Scheme 2

The scheme-3 describes Claisen-Schmidt condensation of the intermediate 1-(3-acetylphenyl)-3-tosylurea (3) with appropriate aromatic/heteroaromatic aldehydes in ethanolic KOH solution (100%) to give the corresponding diaryl sulfonyl urea-chalcone hybrids (4) in good yield[10].



Scheme 3

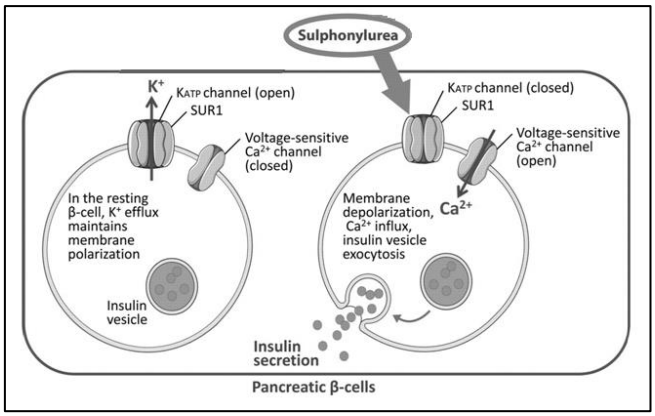
Therapeutic aspects of sulfonylurea

From the extreme literature survey, it was found that sulfonylureas have different types of activity along with antidiabetic activity. The different researcher reported some of the activities like antidiabetes, anticancer, diuretic. anti-inflammatory, antimalarial, antitubercular etc.

Some of the case studies are described below

Sulfonylureas as Antidiabetic agent

Sulfonylureas stimulate insulin secretion from pancreatic β-cells and are widely used to treat type 2 diabetes. The principal target of sulfonylureas is the ATP-sensitive potassium (KATP) channel, which plays a major role in controlling the β-cell membrane potential. Inhibition of KATP channels by sulfonylureas causes depolarization of the β-cell membrane; which in turn, triggers the opening of voltage-gated Ca^{2+} channels by eliciting Ca^{2+} influx and a rise in intracellular Ca^{2+} to stimulates the exocytosis of insulin-containing secretory granules[11].



HB Zhang et al reported excellent hypoglycemic activity and antithrombotic property of some sulphonylurea derivative. The reported compound can be used in the treatment of diabetics with cardiovascular and nephropathy complications. The target compound affects the insulin release of isolated rat pancreatic islets and the glucose transport in adipocytes of rats [12].

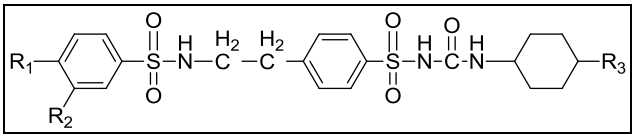


Figure 2

Jawale DV et al developed a series of new 2,4-thiazolidinediones with aryl sulfonylurea moieties as antihyperglycemic agent [13].

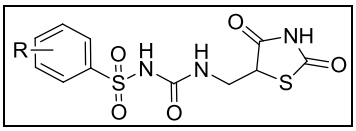


Figure 3

The potent oral antihyperglycemic activity of pyridazinone substituted benzene sulfonylurea derivatives was reported by Ratish I G et al, The reported compound completely prevented the rise of blood glucose of NIDDM rats as compared with NIDDM control [14].

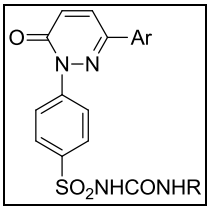


Figure 4

Thakur AS et al, reported a new series of 3-(4-substituted phenyl)-1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenyl sulfonyl)-1-substituted urea. The hypoglycemic effect was studied using oral glucose tolerance test in normal and NIDDM in STZ-rat model. All the fifteen derivatives were shown a very prominent oral hypoglycemic effect at the dose of 40 mg/kg body weight (p.o.) in respect of standard drug glibenclamide and control [15].

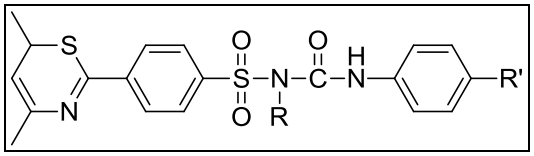


Figure 5

Faidallaha HM *et al* 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 [16].

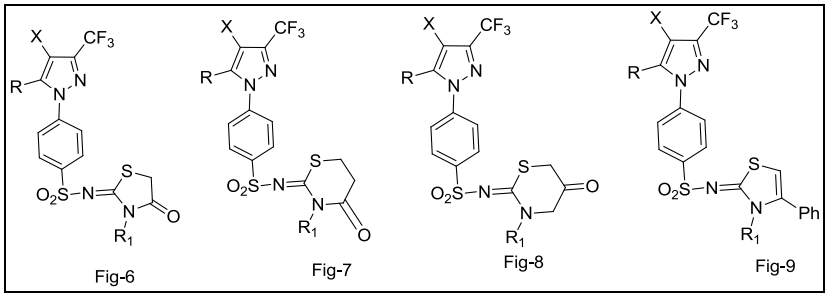


Figure 6-9

Sulfonylureas as anticancer

From the literature it was found that glibenclamide is one of the derivatives which has anticancer activity.The study was carried out on different cancer types at the preclinical level. The role of glibenclamide as KATP channel inhibitor and its interaction with ROS (Reactive Oxygen Species) production seem to responsible for the antitumor effect.

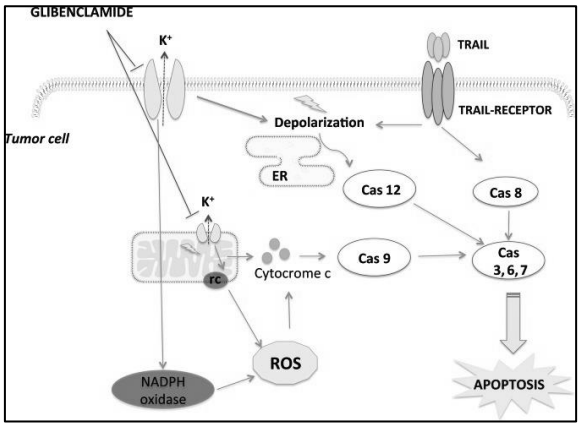


Figure: 10

Glibenclamide increases NADPH oxidase and mitochondrial respiratory chain ROS production followed by the release of proapoptotic factors and caspase activation. Membrane depolarization by glibenclamide and TRAIL (Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand) induces ER (Endoplasmic Reticulum) stress-mediated apoptosis. Glibenclamide sensitizes tumor cells to TRAIL-dependent apoptosis through membrane depolarization and ROS production [17]. A series of 3-(4-chlorophenyl)-[1,2-c]pyrazol(in)es-substituted with benzenesulfonamides, N1,N3-disubstituted sulfonylurea and sulfonyl thiourea pharmacophores, and some derived thiazolidinedione and thiazoline ring systems were evaluated for their antitumor activity by Rostom Sherif AF et al. The reported compounds showed promising broad spectrum antitumor activity against most of the tested subpanel tumor cell lines [18].

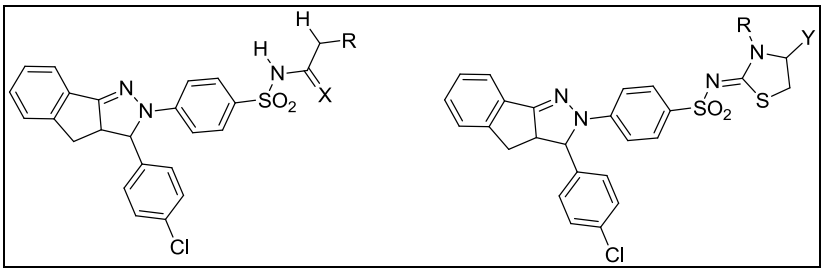


Figure: 11,12

Zhi-Jun Zhang et al, synthesized three series of novel sulfonylurea podophyllotoxin derivatives which are evaluated for in vitro cytotoxicity against four tumor cell lines (A-549, DU-145, KB and KBvin). Compounds showed superior cytotoxic activity compared with etoposide [19].

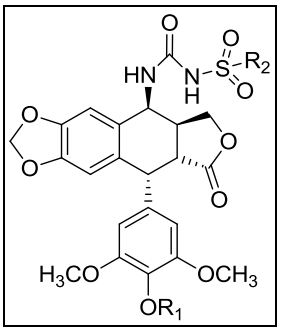


Figure: 13

Hassan MF *et al*, reported in vitro antitumor activity some new benzenesulfonamides, disubstituted sulfonylureas, and sulfonyl thioureas. The compounds were substituted basically with 3-(2-thienyl or 3-pyridyl)-indeno[1,2-c]pyrazol(in)e [20].

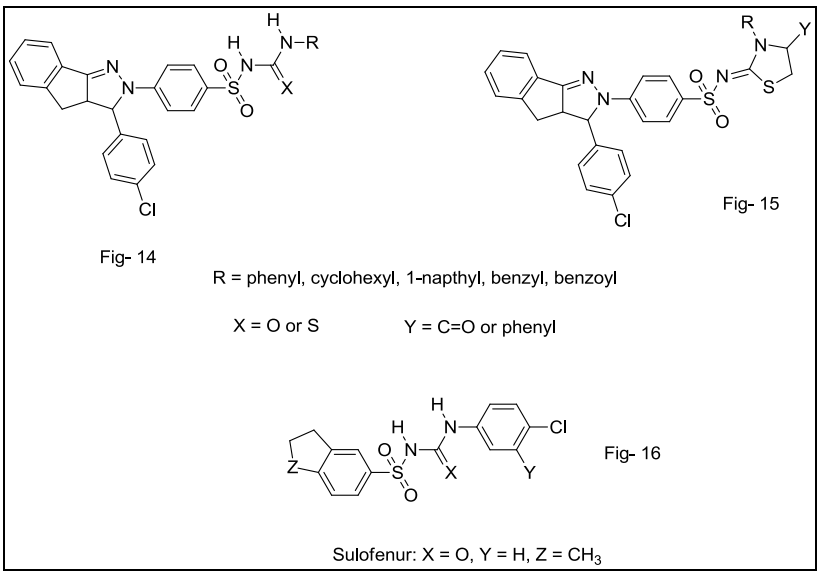


Figure 14-16

Szafrański K et al synthesized a series of novel 4-substituted-N-(phenyl carbamoyl)-3-pyridinesulfonamides. The in vitro anticancer activity of the compound was evaluated. The reported compound has exhibited a good activity profile and selectivity toward the subpanels of leukemia, colon cancer, and melanoma, with average GI50 values ranging from 13.6 to 14.9 μM [21].

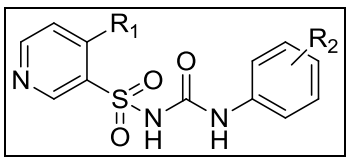


Figure 17

Sulfonylureas as diuretics

Torasemide (rINN) or torsemide (USAN) is a pyridine-sulfonyl urea type loop diuretic. The actions of torsemide can be mediated by several mechanisms operating within the thick, medullary segment of ascending loop of henle. These include interference with Na+/K+/2Cl– co-transporter at the luminal surface; Na–K pump and anion exchange [22].

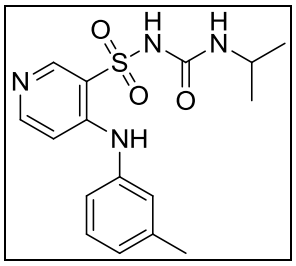


Figure 18

Sulfonylureas as anti-inflammatory agents

Recently, a wide range of anti-inflammatory effects of glibenclamide has been reported in different articles. Some of them are reported here.

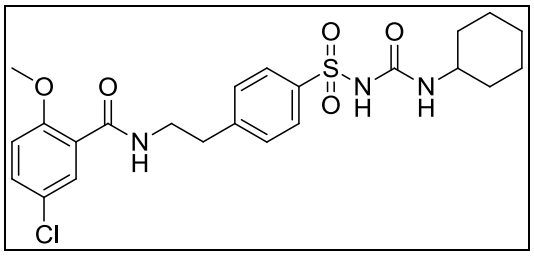


Figure 19

Simard et al had reported that glibenclamide was highly effective in reducing several short-term effects of SAH (Subarachnoid Hemorrhage), including barrier disruption, caspase-3 activation, inflammation and vasogenic edema [23]. Cui W et al using OVA (ovalbumin) induced mouse model of asthma. He evaluated the effects of glibenclamide on the AHR (Airway Hyperresponsiveness) and inflammation. Glibenclamide reduced all the cardinal features of asthma in OVA-challenged mice, including AHR, airway inflammation, and T-helper type 2 (Th2) cytokines [24]. Koh et al studied a case of 1160 patients with gram-negative sepsis and present observational evidence for a glyburide-associated benefit during human melioidosis and correlate this with an anti-inflammatory effect of glyburide on the immune system. The study showed that survival was greater in diabetics than in nondiabetics (38% vs 45%, respectively, P 5.04), but the survival benefit was confined to the patient group taking glyburide [25]. Cai J et al concluded that glibenclamide could attenuate myocardial injury induced by LPS (Lipopolysaccharides) challenge in streptozotocin-induced mice, which was possibly related to inhibiting inflammation through Nalp3 inflammasomes. Glibenclamide pretreatment significantly inhibited the serum levels of pro-inflammatory cytokines. Glibenclamide treatment also suppressed the increase of IL-1β (Interleukin-1β) level induced by high glucose and LPS. Furthermore, Nalp3 and Caspase-1 levels were markedly increased by high glucose plus LPS, and both proteins were significantly inhibited by glibenclamide treatment [26].

Kewcharoenwong C et al, had collected purified PMNs (polymorphonuclear neutrophils) from diabetic patients who had been treated with glibenclamide. The result revealed that reduction of interleukin IL-1β and IL-8 secretion when exposed to Burkholderia pseudomallei. Additionally, reduction of these pro-inflammatory cytokines occurred when PMNs from diabetic patients were treated in vitro with glibenclamide. These findings suggest that glibenclamide might be responsible for the increased susceptibility of diabetic patients, with poor glycemic control, to bacterial infections as a result of its effect on reducing IL-1b production by PMNs [27].

Sulfonylureas as anticonvulsant and neuroprotective agent

Thakur AS et al, synthesized a newer series of 1-(4-substitutedphenyl)-3-(4-((2,4-dioxothiazolidin-5-lidene)methyl)phenyl sulfonyl)urea/thiourea for their anticonvulsant activity. The activity is characterized by its potential to restrain astrocytic Na+, 2HCl, and K+ co-transport similar to torasemide which has sulfonylurea in

its structure. Torasemide obstructs kainic acid-induced electrical discharges observed from cortex and it has neuroprotective agents, for instance antagonizing the N-methyl-D-aspartate (NMDA) and non-NMDA receptors for evaluating antiepileptic activity. The reported compounds were proved to be effective anticonvulsant pharmacophore [28].

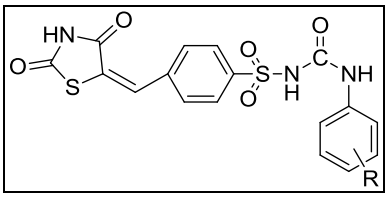


Figure 20

Masereel B et al, reported N-[(4-cycloheptylaminopyrid-3-yl)sulfonyl]-N'-cycloheptyl urea as a neuroprotective agent. The related sulfonyl (thio) ureas were evaluated in the maximal electroshock seizure test in mice. The reported compound exhibited a higher protective index and potency than those of phenytoin [29].

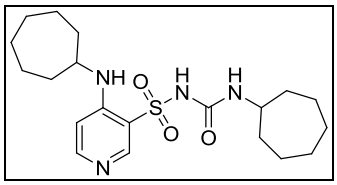


Figure 21

Sulfonylureas as carbonic anhydrase (CA) inhibitors

Claudiu TS et al, developed reaction for nine aromatic/heterocyclic sulfonamides. They are assayed for inhibition of three isozymes of carbonic anhydrase (CA). Good inhibition of all these three CA isozymes was observed with the new compounds, but an exciting finding was that the ureas/thioureas and especially the above-mentioned compound have an increased affinity to the slow isozyme hCA I, generally less susceptible to inhibition by sulfonamides, as compared to the rapid isozymes hCA II and bCA IV [30].

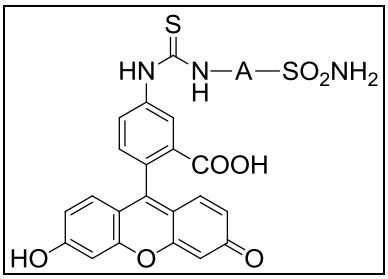


Figure 22

Some other therapeutic effects of sulfonylurea derivatives

15-lipoxygenase (15-LOX) inhibitors

Mahdavi M et al, synthesized a series of 3-aroyl-1-(4-sulfamoylphenyl)thiourea derivatives containing sulfonamide moiety as 15-lipoxygenase (15-LOX) inhibitors. The most potent compound (3- methyl benzoyl derivative) have IC50 value of 1.8 μM. The reported compound was 10-fold more potent than quercetin. Interestingly, it also showed the highest antioxidant activity, as determined by ferric reducing antioxidant power (FRAP) assay [31].

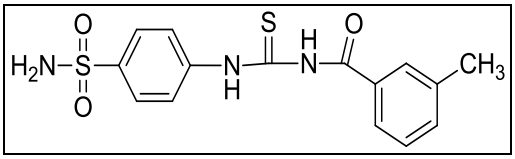


Figure 23

Bugata B K et al synthesized a series of some new diaryl sulfonyl urea-chalcone hybrids via Claisen-Schmidt condensation reaction. All the synthesized compounds were evaluated for their in vitro 5-Lipoxygenase inhibitory activity using potato 5-lipoxygenase enzyme. The tested compounds exhibited significant inhibitory activity at IC50 values [32].

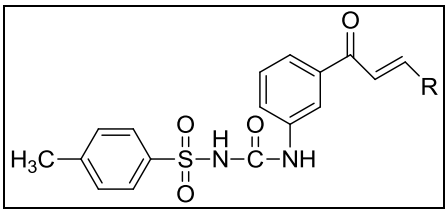


Figure 24

Antimicrobial agents

Faidallaha HM et al, also reported antimicrobial property of fluorinated 1,2,4-triazoles and benzene sulfonylurea and thiourea derivatives as well as their cyclic sulfonyl thioureas compound. 4-oxothiazolidines, thiazolidines, 4,5-dioxothiazolidines and thiazolines. Preliminary biological screening of the prepared compounds revealed significant antimicrobial and mild antidiabetic activities [33].

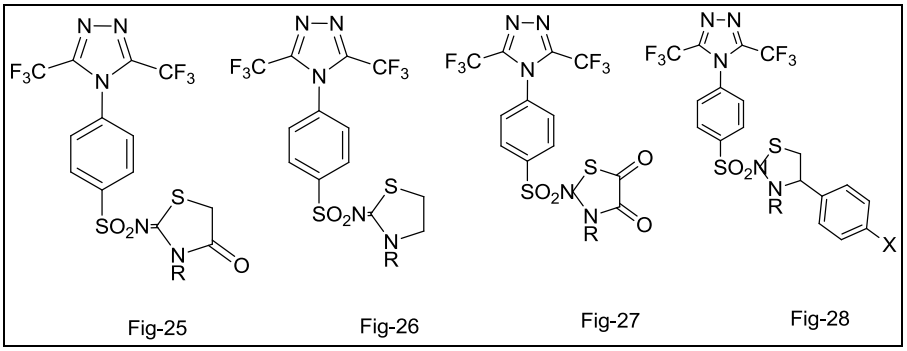


Figure 25-28

Deniz SD et al, synthesized some pyridazine derivatives carrying urea, thiourea, and sulfonamide groups. The synthesized compounds were evaluated for their antimicrobial activity against gram-positive and gram-negative bacteria, and fungi by using broth microdilution. The synthesized compounds exhibited generally promising inhibitory activity against S. aureus and E. coli. Moreover, all compounds showed antifungal activity against both C. albicans and C. parapsilosis, with a MIC value of 8 μg/mL [34].

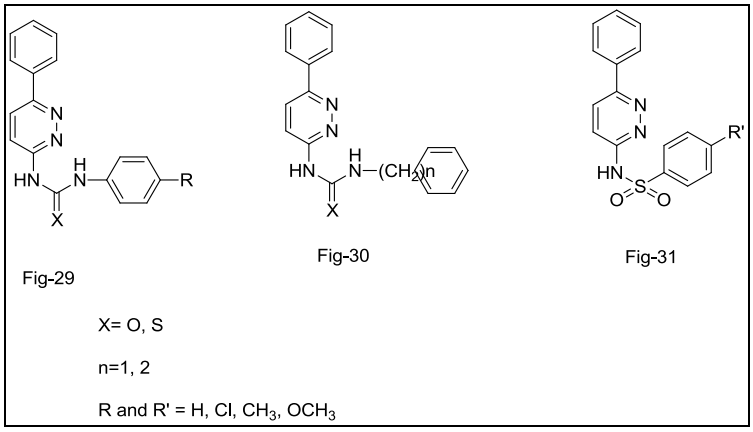


Figure 29-31

Antitubercular activity

Li Pana et al, had reported a series of novel monosubstituted sulfonylurea derivatives. They found to have activity against Mycobacterium tuberculosis H37Rv in vitro. Both the compounds displayed good antituberculosis activities (MIC 10 mg/L), which were comparable with that of the sulfometuron methyl [7].

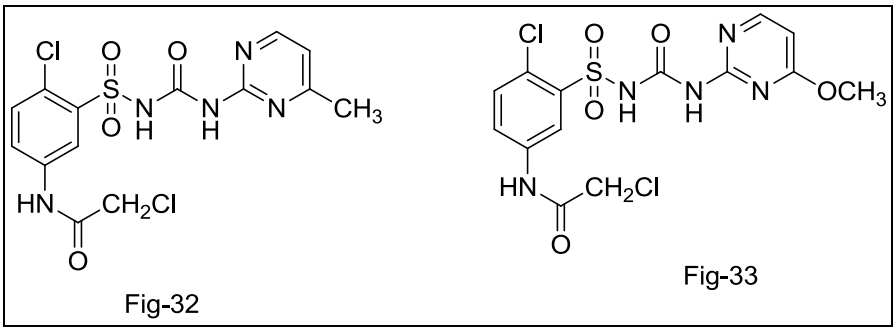


Figure 32-33

Antimalarial Activity

Leon CI et al had developed a series of sulfonylureas and tested their antimalarial activities. The Study also included the inhibition of in vitro development of a chloroquine-resistant strain of Plasmodium falciparum, in vitro hemoglobin hydrolysis, hemozoin formation, and development of Plasmodium berghei in murine malaria. The most active antimalarial compound was (E)-1-[4′-(3-(2,4-difluorophenyl)acryloyl)phenyl]-3-tosylurea (fig-35) with an IC50 of 1.2 μM against cultured P. falciparum parasites [6].

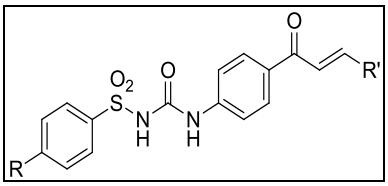


Figure 34

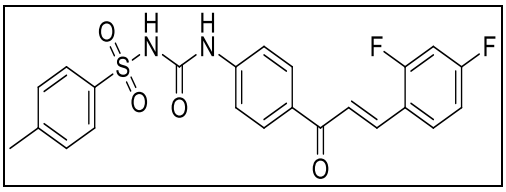


Figure 35

CONCLUSION

From the above discussion, it can be concluded that the various methods had been reported for the preparation of sulfonylureas derivatives. It can be prepared by chloro- sulfonation and amidation between sulfonamides and isocyanates. Beside this Claisen-Schmidt condensation is also a reported reaction for the preparation of sulfonylurea. The literature also proves the pancreatic and extrapancreatic effect of sulfonylureas. They have an extrapancreatic effect like, diuretics, anti-inflammatory, anticancer, antimalarial etc.

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