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EXPLORING THE SAR AND BIOLOGICAL ACTIVITIES OF SULFONYLUREA DERIVATIVES: A REVIEW

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ABSTRACT

Marcel Janbon made the first discovery of sulfonylureas in 1942 as hypoglycemic agents. This review thoroughly investigates the biological activities of sulfonylurea derivatives, including their modes of action and therapeutic potential. The sulfonylurea class has three generations, each with improved potency and specificity in controlling insulin secretion via pancreatic β-cell receptors. Beyond their antidiabetic characteristics, sulfonylureas show promise as anticancer medicines, with derivatives blocking ectonucleotidases and increasing chemo sensitivity in malignancies. Their efficacy extends to antibacterial, antitubercular, antimalarial, antifungal, anti-inflammatory and anticonvulsant applications, with structural changes having a substantial impact on their activity. Additionally, sulfonylureas have demonstrated potential as diuretics, carbonic anhydrase inhibitors and 5-lipoxygenase inhibitors, opening up new treatment pathways. The review focuses on the structure-activity relationship (SAR) studies that support these various pharmacological activities, emphasizing the importance of functional group changes. This diverse biological profile establishes sulfonylureas as critical chemicals in medication development, necessitating additional research into their molecular processes and therapeutic implications.

KEYWORDS: Sulfonylureas, derivatives, biological activities, the structure-activity relationship (SAR), pharmacological activities.

INTRODUCTION

Drugs called sulfonylureas are used to treat diabetes. It is employed to release insulin into the bloodstream. Sulfonylureas discovered by Marcel Janbon in 1942. He experimented on sulfonamide antibiotics and developed sulfonylurea, which reduced sugar levels in animals. Although it doesn't make insulin, it does cause the blood to secrete more of it. In 1960, several sulfonylureas were found and classified into three classes. First, second and third generations. By raising the amount of insulin secreted by the pancreas, the first generation lowers blood glucose levels. Second generation is more potent than the previous generation. It is taken once daily at a reduced dosage. Due to its poor potency and medication interactions, first generation is rarely used. Third generation exhibits fewer medication interactions and is more powerful.[1] Sulfonylurea derivatives have a core S-aryl sulfonylurea structure with a p-substitute on the phenyl ring (R1) and several groups terminating the urea at the N′ end group (R2). It is easy to install aryl sulfonamides (R1-C6H4-SO2NH2) chemically by reacting with isocyanates (R2-NCO).[2] These substances also shows various biological activities, such as antidiabetic, anti-inflammatory, anti-cancer, antimalarial, antibacterial, diuretic, antitubercular and antihistamine H3 receptor effects.

Classification

There are three generations of sulfonylureas.

Sulfonylurea structure

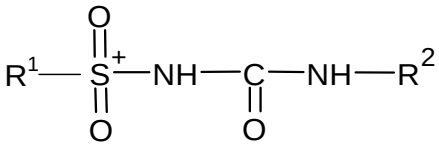


Fig. 1: Sulfonylurea general structure.

1. R1 have an aromatic ring with substituents and be lipophilic. Paraposition is required for the substituents. Potency decreases with smaller substituents and increases with larger substituents.
2. The position of R2 must have a lipophilic nature. In the R2 position, N-methyl group is inactive. Lower activity is given by N-ethyl. Also inactive with N-dodecyl and higher. Potency is highest when N-propyl to N-hexyl is used.

- **First generation of sulfonylureas:** R1 and R2 positions have minor substitutions, resulting in less potency.

  Examples: Tolbutamide, Chlorpropamide, Tolazamide

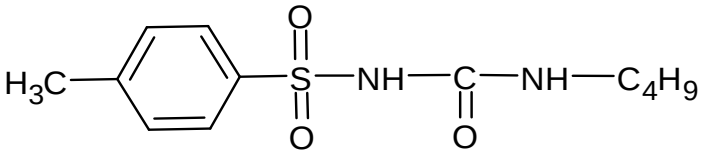


Fig. 2: Tolbutamide.

- **Second generation of sulfonylureas:** R1 and R2 are more potent than first generation since they have bigger substituents.

Examples: Gliclazide, Glipizide, Glyburide, Glibenclamide

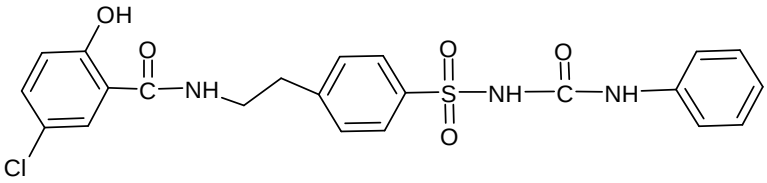


Fig. 3: Glibenclamide.

- **Third generation of sulfonylureas:** Compared to first and second-generation, R1 and R2 have bigger substituents. Thus, it has more potency than the first and second generations.

Examples: Glimepiride

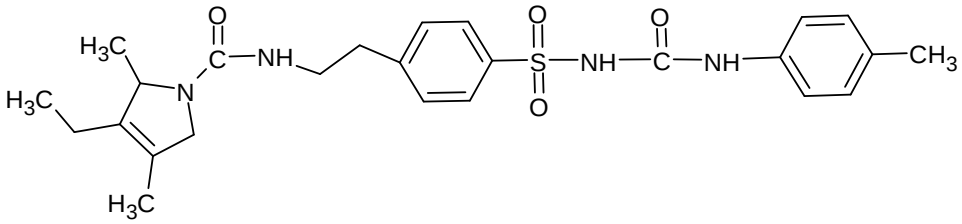


Fig. 4: Glimepiride.

Mechanism of action of sulfonylureas

Sulfonylureas attach to the sulfonylureas receptor on the β-cells of the pancreas. Thus K+ ion channel closes, in order to prevent the k ion from escaping the cell. Depolarization takes place. Consequently, the Ca channel opens, allowing the Ca ions to enter the cells. Moreover, elevated calcium levels in cells cause insulin to be secreted into the bloodstream, lowering blood sugar levels. Fig. 5 demonstrates the mechanism of action of sulfonylureas.

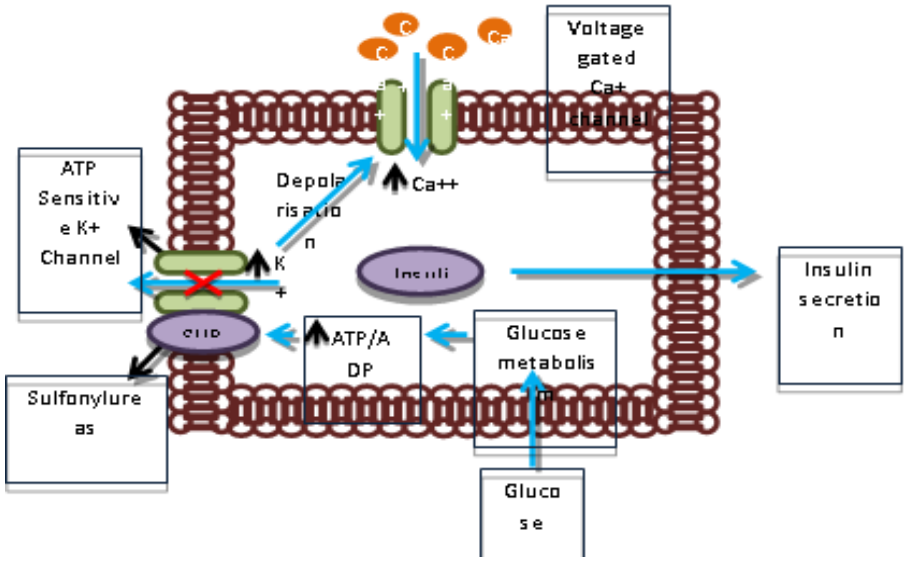


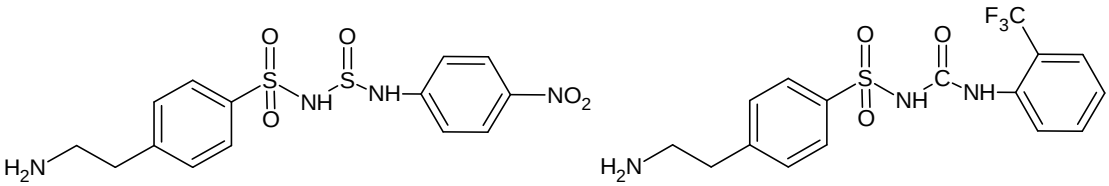
Fig. 5: Mechanism of action of sulfonylureas.

Biological activities

1. Sulfonylureas as anticancer agents

1.1 Crucial metabolizing enzymes called ectonucleotidases help in dephosphorylation of various nucleotide and nucleoside forms. Alkaline phosphatases, ecto-5-nucleotidase, ecto-nucleoside triphosphate diphosphohydrolases and ectonucleotide pyrophosphatase/ phosphodiesterase are all members of the ectonucleotidases class. Altered calcification, proliferation of cells, metastasic disease, aortic calcification, neurology disorder and immunological abnormalities are among the internal difficulties caused by over expression of these enzymes. The efficacy of a number of compounds with the scaffolds of pyridine-pyrazole-benzene sulfonamide or pyridine-pyrazole-benzene thiourea and also pyrrolo-pyridine to block the human isozymes i.e., ENPP1 and ENPP3 was evaluated. The anti-cancer potential of several sulfonylthiourea derivatives and disubstituted sulfonylurea was investigated in earlier studies. The evaluated compounds (Table: 1) have been found to exhibit promising anti cancer action against multiple cell lines, along with excellent inhibitory potency against ENPP1 and ENPP3. Compound 6b to be the most effective inhibitor of h-ENPP1 identified in earlier investigation of h-ENPP1, h-ENPP3 and ecto-5-nucleotidase with an IC50 value of 0.11±0.01μM, 0.79$\pm$0.02 and 7.12$\pm$1.3. While compound 6d to be the most effective inhibitor of h-ENPP3 with an IC50 value of 0.038±0.02μM. The presence of nitro group at the position 4 to the benzene ring and the group trifluro methyl contributed to the effectiveness of substances 6b and 6d (Fig. 6). With an IC50 value of 0.83±0.01μM compound 7a (Fig. 7)

against h-ecto-5-nucleotidase and 0.26±0.05µM compound 6b against r-ecto-5C-nucleotidase was the most effective.



6b **6d**

Fig. 6: Most effective sulfonylurea derivatives.

Propyl, which has a little electron donating effect demonstrated moderate activity against h-ecto-5-nucleotidase in case 7a, where as nitro phenyl which is an electron-withdrawing group in case 6b has a very promising inductive effect on aromatic rings and resonance which increases the compound overall inhibitory potency. Propyl groups were found to be selective inhibitors of h-ecto-5C-nucleotidase and contributed to compound 7a selectivity. The MTT assay was done to identify the potential of anti-proliferation of cells of sulfonylurea produced derivatives on baby hamster kidney fibroblasts (BHK-21) cells and human breast cancer cell line (MCF-7) at a concentration 100µM of the compound. As a result the compound 6b shown maximum percentage cytotoxicity compared to doxorubicin.[3]

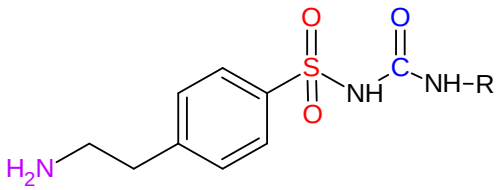


Fig. 7: Compound aginst h-ecto-5C-nucleotidase.

Table 1: Sulfonylurea and Sulfonylthiourea derivatives.

Compound	R	IC50±SEM (µM) or Inhibition			
		h-ENPP1	h-ENPP3	h-e5NT	r-e5NT
7a	C_3H_7	29%	32%	0.83±0.01	31%
6b	4-$NO_2(C_6H_4)$	0.11±0.01	0.79±0.02	7.12±1.3	0.26±0.05
6d	2-$CF_3(C_6H_4)$	0.42±0.02	0.038±0.02	17.1±0.47	49%
Suramin	-	7.80±0.09	0.89±0.16	18.54±1.14	12.83±0.23

ATP-dependent potassium ion channels and ATP binding cassette transporters are blocked by glibenclamide, which also makes tumors more sensitive to chemotherapeutic medications according to anti cancer mechanisms. Tumor growth, cell cycle progression and cell migration are all suppressed and ROS (reactive oxygen species) are produced which

ultimately causes cancer cells to undergo apoptosis. Glibeclamide may therefore be used to treat patients with ovarian, cutaneous, stomach and lung malignancies. Fig. 8 Schematic representation of anti-cancer and anti-diabetics sulfonylureas. Fig. 8 describes the schematic representation of anti-cancer and anti-diabetics sulfonylureas.[4]

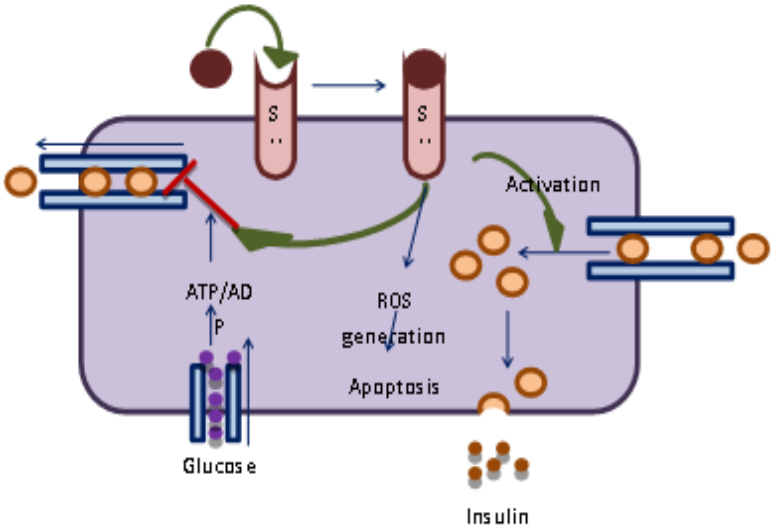


Fig. 8: Schematic representation of Anti-cancer and Anti-diabetics sulfonylureas.

1.3 The pyridine ring or phenoxy group was the primary target of these compounds. When sulfonylurea units were used in place of urea scaffolds in a prior work the resultant derivatives demonstrated moderate effectiveness as inhibitors of VEGFR2/KDR.[5] First in order to study the substituents for the activity, various replacements were done at the aryl moiety. A fluorine atom was also added to the phenoxy group, which was motivated by the c-Met kinase inhibitory effects of regorafenib, KI8751 and derivatives of 6,7-disubstituted-4-phenoxyquinoline that were observed in prior investigations. Table 2 displayed the compounds in Fig. 9a–k structures and design approach.[6]

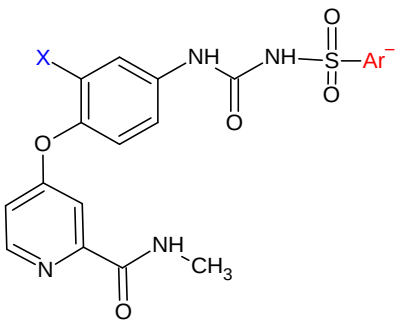
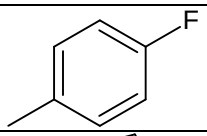
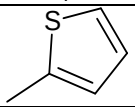
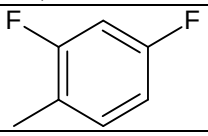
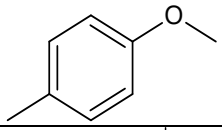
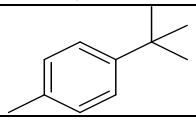
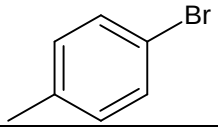
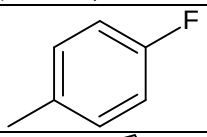
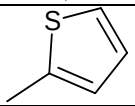
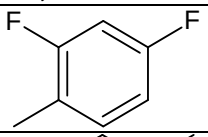
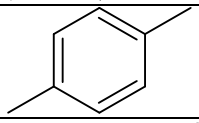
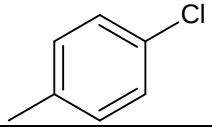


Fig. 9: Compounds 9a–k structures.

Table 2: Compounds 9a-k activity and structures.

Compound No.	X	Ar	Inhibitory rate of VEGFR2/KDR at 10μM	IC50 (μM)			
				Hela	A549	MCF-7	PC-3
9a	H		23.6% ± 12.9%	>100	>100	>100	>100
9b	H		54.0% ± 2.7%	>100	65.86 ± 2.01	72.43 ± 1.96	>100
9c	H		75.8% ± 5.5%	>100	27.04 ± 1.43	>100	25.35 ± 1.73
9d	H		61.3% ± 9.6%	>100	86.91 ± 2.03	80.56 ± 2.04	>100
9e	H		31.4% ± 7.2%	>100	>100	>100	68.87 ± 2.14
9f	H		46.6% ± 1.8%	63.92 ± 1.81	32.59 ± 1.51	16.54 ± 1.22	17.97 ± 1.56
9g	F		<20.0%	42.43 ± 1.93	>100	17.19 ± 1.54	ND
9h	F		<20.0%	>100	>100	>100	ND
9i	F		<20.0%	>100	57.42 ± 1.89	>100	ND
9j	F		<20.0%	24.65 ± 1.69	33.22 ± 1.82	>100	ND
9k	F		<20.0%	44.32 ± 1.75	>100	69.25 ± 1.96	ND
Sorafenib	-	-	94.9% ± 1.1%	8.08 ± 0.91	6.53 ± 0.82	4.21 ± 0.62	11.05 ± 1.07
Staurosporine	-	-	97.3% ± 2.82%	ND	ND	ND	ND

1.4 Glibenclamide is a potassium channel blocker that kills cancer cells by generating reactive oxygen species (ROS) and free radicals. Furthermore, pro-apoptotic action is shown against cancer cells by diaryl sulfonylureas (DSU) that are resistant to several

drugs. It exhibits anti tumor efficacy, according to preclinical and clinical research. Both tumor growth and cancer cell proliferation can be inhibited by it. It also has the ability to suppress angiogenesis and metastasis. According to earlier research, the second generation is more powerful than the first. Compared to the first one, it has more anti cancer effects. Fig. 10 describes the MOA of glibenclamide.[7]

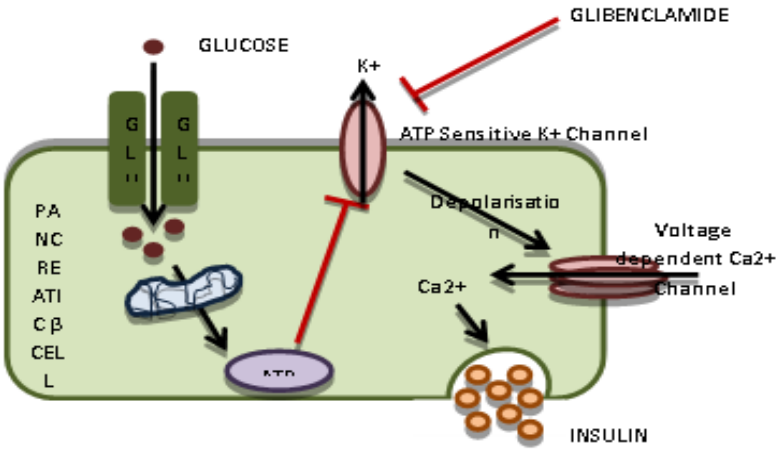


Fig. 10: MOA of glibenclamide.

1.5 The impact of new sulfonylurea derivatives on the HePG2 cell line has been examined in earlier laboratory experiments. With an IC50 of 4.25µM against the HePG2cell line, the 4-methyl-N- ((3-propionyl-4,5,6,7-tetra hydro benzo [b] thiophen-2-yl) carbamoyl) benzene sulfonamide) Fig. 11 demonstrated strong anticancer activity in comparison to the reference medication i.e., 5-fluoro uracil, which had an IC50 of 316.25Mm.[8]

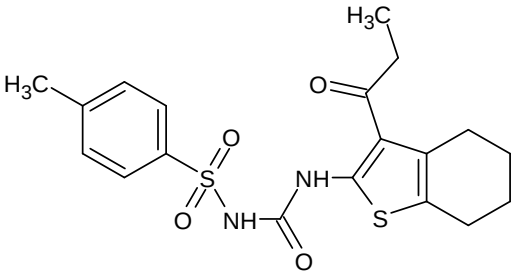


Fig. 11: Sulfonylurea as anticancer derivative.

1.6 Compounds 12a and 12b also found strong cancer inhibitory properties. The majority of drugs with an unsubstituted phenyl group demonstrated both strong *in vivo* antidiabetic efficacy and the highest docking score. However, there was no discernible trend in either activity or docking score for substitution on the aryl ring connected to the urea/thio urea connection. Even when the docking score was high, the *in vivo* antidiabetic efficacy was

considerably reduced when bulky aryl groups, such as anthracene, were substituted. *In vivo* activity was nearly as substantial when the thiophenyl ring was substituted for the aryl ring as when the benzyl ring was substituted. In contrast to the unsubstituted thiophenyl ring, the methyl group substitution did not significantly alter the thiophenyl ring. The *in vivo* antidiabetic efficacy and dock score were considerably reduced when urea linkage was substituted with thiourea linkage. The mean growth percentages for these substances 12a and 12b were 89.29% and 87.76%, respectively. With growth percentages below 62%, both of these compounds (MALME-3M, M14, MDA-MB-435, SK-MEL-28, SK-MEL-5, UACC-257, and UACC-62) shown minimal sensitivity to melanoma. Additionally, compound 12b showed a strong sensitivity (5.45%) to the A549/ATCC cell line, which is derived from non-small cell lung cancer.[9]

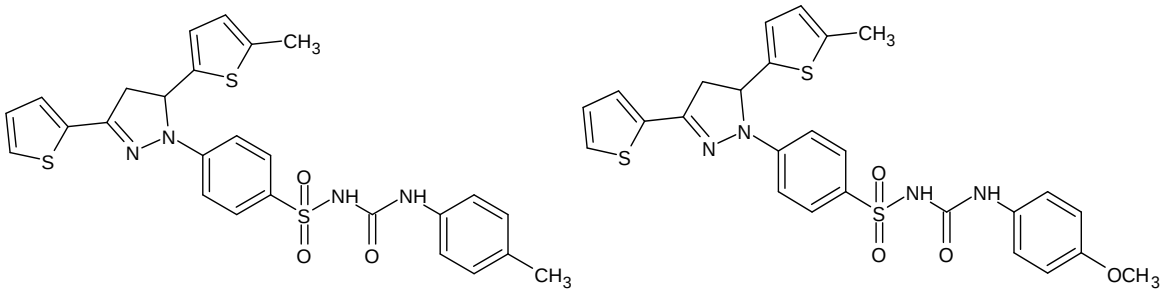


Fig. 12: Compounds 12a and 12b with strong cancer inhibitory properties.

1.7 Preparation *in vitro*, *in silico* and SAR investigations the trifluoromethyl group or CF3, the most prevalent hydrophobic functional group. It is bulkier than the methyl group. Trifluoromethyl substituents influence the electronic characteristics of the aromatic rings. Hence the best reported medications with an trifluoromethyl groups which is aromatic in their structure, examples include Casodex (also known as Bicalutamide, an anti tumor drug) and Januvia (a medication prescribed to treat the symptoms of blood sugar disorder). The trifluoromethyl substituent is frequently included in order to increase potency through the establishment of multiple interactions with the carbonyl groups of the targeted protein. Several urea compounds, notably the alkylating agent medication N-nitrosourea found to have cancer inhibiting properties. Additionally, by causing reactive oxygen species (ROS) and subsequent cancer cell apoptosis, glibenclamide, a sulfonylurea demonstrated its ability to limit tumor growth. It is found to be true that a compound biological activity will be increased when it contains a urea moiety and aromatic trifluoromethyl replacements. The sulfonyl group in compound is necessary to

boost their anti cancer properties when compared to compound which do not include the sulfonyl group. The illustration of Sulfonyl-urea derivatives 13a-e (Fig. 13).[10]

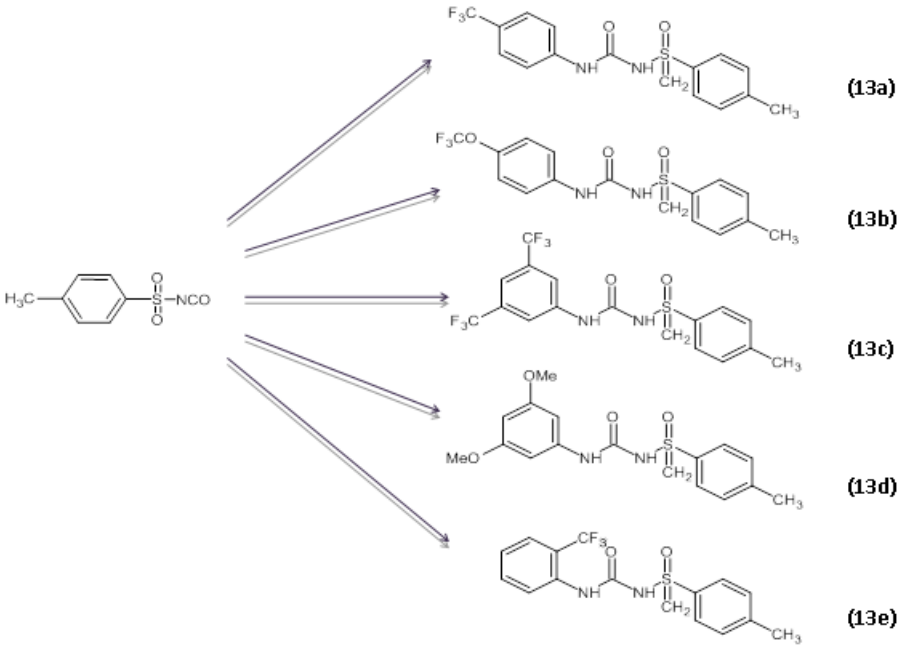


Fig. 13: Illustration of sulfonyl-urea derivatives 13a-e.

2. Sulfonylureas as antituberculosis agents

As antituberculosis medicines, monosubstituted sulfonylurea derivatives, sulfonylurea and imidazolinone, two identified inhibitors of plant AHAS (aceto hydroxyl acid synthase) long been used extensively and effectively as commercially available herbicides. Some sulfonylurea compounds including sulfometuron methyl (SM), chlorimuron ethyl (CE) and metsulfuron methyl (MM) *invitro* found to shown strong activity against TB strains according to earlier studies that examined the bacteriostatic activity of plant AHAS inhibitors in resistance to the TB. Sulfonylureas are characterized by a core sulfonylurea bridge that has a heteroaromatic ring linked to the nitrogen moiety and an ortho substituted aromatic cycle linked to the sulphur moiety. The connection between sulfonylurea structure and anti-TB activity, the heterocycle tail structure and aromatic back bone of those derivatives are thought to be responsible for the variations in anti-TB activity. All of the molecules they studied however had the hetero cycle ring system substituted in both m-positions. In addition to finding that monosulfuron and monosulfuron ester (both containing 4-monosubstituted pyrimidine) have detectable effectiveness in opposition to TB. Earlier research demonstrated that certain sulfonylurea derivatives having only one substituent at m-position on the hetero cycle ring showed significant and unusual AHAS antagonistic activities. 25 new sulfonylurea compounds were created, produced and examined to identify the mycobacterial inhibiting

properties in opposition to the common TB strain H37Rv. These substances had four monosubstituted pyrimidines changed at the C5-substituted acyl aniline. Using the MIC, five novel compounds were found to possess anti mycobacterial properties. Table 3 showed the title compounds 14a,b,c,d,e lowest inhibitory concentrations (MIC) against H37Rv. With MIC values of 10mg/L, the most active drugs were 14a and 14d and they showed the same effectiveness as the sulfometuron methyl that was examined in prior investigation.

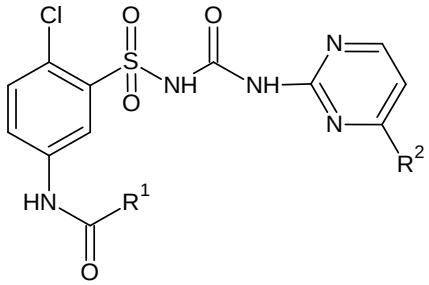


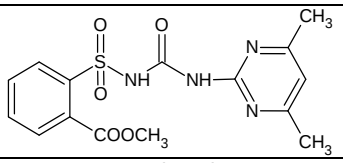
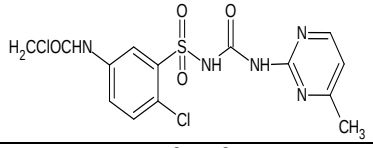
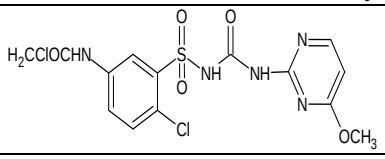
Fig. 14: Compounds with anti-TB activity.

Table 3: The MIC of the compounds against H37Rv.

Compounds	R1	R2	MIC for H37Rv (mg/L)
14a	CH2Cl	CH3	10
14b	CH=CH2	CH3	20
14c	C6H5	CH3	100
14d	CH2Cl	OCH3	10
14e	CH=CH2	OCH3	40

The discovery that derivatives 14a and 14d have the identical CH2Cl moiety was unexpected, this could be due to the inductive action of a one chlorine group. The action is eliminated when the R1 is substituted with an alkyl group, ester group or fluoro alkyl group. The MTT assay was used to assess 14a and 14d suppression of cellular viability opposition to THP-1 cells in order to ascertain whether they had harmful effects on mammalian cells. Having an IC50 in opposition to THP-1 cells of over 100mg/L (14a: 137.92mg/L, 14d: 179.70mg/L) measured 72 hours after substances were included each of the two compounds shown negligible cytotoxicities. This is ten times higher than the MIC's of both substances on the *M. tuberculosis* strains.[11] Doses of 500mg/kg were initially used to assess the drugs *invivo* efficacy (Table 4). Mice treated with compounds a and b were more effective at this concentration because 250mg/kg dosages of these compounds significantly reduced the number of live bacteria, while treatment with SM only slightly altered the quantity.[12]

Table 4: MIC and structure of novel sulfonylurea compound.

Compound	Structure	MIC for H37Rv (mg/L)	Intra cellular inhibition (%) at 50mg/L	Reference
Sulfometuron methyl		10	70.1±6.6	3,4,9
a		10	66.6±9.5	9
b		10	64.4±8.8	9

3. Sulfonylureas as anti malaria agents

The sulfonylurea moiety a,b-unsaturated keto function, a crucial component of antimalarial action. Furthermore, when paired with an a,b-unsaturated ketone bridge certain pharmacophoric groups with antimalarial properties found in sulfonylurea derivatives may have an additional impact. They examined the compounds capacity to prevent the production of hemozoin. The most potent compound 15b (Fig. 15), inhibited haemoglobin breakdown by 90.28% at a 5 mM dosage and mice which was affected with *P. berghei* on derivatives with inhibitory activity ranging from 53 to 85% evaluated against to control. The chemical 1[40-N[N0(400-chlorosulfonyl)urenyl]phenyl] was the most active. 2-propen-1-one (3(3,4-methylenedioxyphenyl). Some electrical interactions between the medication and the biological substrate may be the cause of its activity.

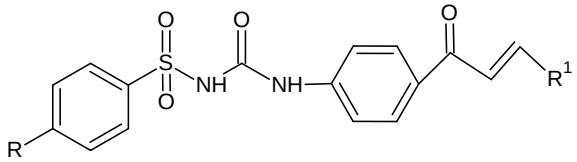


Fig. 15: Sulfonylurea derivative with anti-TB activity.

Table 5: Compounds showing strong anti malaria effects.

Compound	R	R^1	Yield (%)	Mp	Formula	Analyses
15a	Cl	2,4-diFC_6H_3	89	326	$C_{22}H_{15}Cl\ F_2N_2SO_4$	C, H, N
15b	Me	2,4-di$F\ C_6H_3$	91	320	$C_{23}H_{18}F_2N_2SO_4$	C, H, N

Table 5 shows that -3-tosylurea (15b) had the strongest malarial inhibitory activities with IC50 values of 2.1 and 1.2 mM respectively. They identified that the 2,4-difluoro substituted substances found on the aromatic cycle of a,b-unsaturated ketone system are crucial for mediating action against *P. falciparum* in light of the result. Stronger chemical contact with the biological substrate may result from the aromatic ring difluoride atom. In a *P. Berghei* mouse model, compound 15a was equally very efficacious with a 77% decrease in parasite burden four days post-infection and a corresponding increase in survival. Their findings provide compelling evidence that compound 15b is best choice, indicating that it may be exhibiting antimalarial activity *in vitro* by preventing hemoglobin breakdown and hemozoin production. These findings also imply that it is probably going to provide a good antimalarial drug, particularly for sulfonylurea derivatives with fluorine substitution in the aromatic ring.[13]

4. Sulfonylureas as antifungal agents

4.1 The initial enzyme in the branched-chain amino acid biosynthesis pathway, plant acetohydroxyacid synthase (AHAS), is inhibited by sulfonylurea herbicides. Prior research has demonstrated that deleting the AHAS gene in *Candida albicans* results in a reduction in virulence, indicating that AHAS could be a target for antifungal medications.

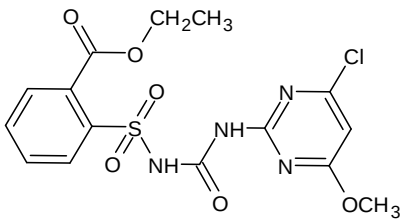


Fig. 16: Chlorimuron ethyl (CE).

The capacity of the eight marketed sulfonylureas to stop *Candida albicans* growth in disk diffusion experiments and cell culture was evaluated. With a 2 μM of MIC50 in contrary to *Candida albicans*, CE (Fig. 16) is the most active molecule. Another sulfonylurea Having an Ki value of 20 nM that effectively inhibits *C. albicans* AHAS is ES. Having an MIC50 of 2 μM, it also shows effective performance against *Candida albicans* in cell growth system. On the basis of CE structure, derivatives of sulfonylureas were created, synthesized and evaluated as *C. albicans* AHAS inhibitors in earlier studies and to ascertain how they affected *C. albicans* growth in cell assays tests. The design was based on changing the groups X and R on the ring systems with hetero atoms and conjugated aromatic cores, respectively (Fig. 17). The only possible modifications in the X position is to swap out the chlorine atom for an

iodine or bromine atom. Although there wouldn't be any more room within this site to hold an additional atom, it was thought that binding would benefit from an ionic radius that is larger than that of chlorine. The modification of site R also involved the substitution of iodine, bromine or hydroxyl for a hydrogen moiety attached to the methyl at the terminal position or the addition of one methyl group to shorten the group. It was anticipated that the hydroxyl group would form a beneficial hydrogen bond with Q202 side chain. In an effort to help carry the sulfonylurea derivatives into the mycological cell, three molecules with a non-polar segment linked to the hydroxyl group were also created.

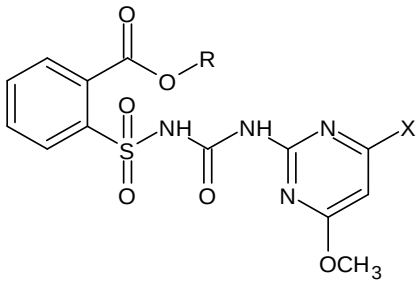


Fig. 17: Sulfonylurea derivative with antifungal activity.

Table 6: Molecules as *C. albicans* AHAS antagonists.

	R	X	K_i (nM)	MIC_{50} (µM)	MIC_{50} (µg/ml)	MIC_{90} (µM)	MIC_{90} (µg/ml)
17a	CH_2CH_3	I	3.8 ± 0.5	0.6 ± 0.2	0.30	1.56	0.78
17b	CH_2CH_3	Br	4.1 ± 0.6	0.7 ± 0.2	0.36	1.56	0.72
17c	CH_3	I	3.9 ± 0.8	1 ± 0.5	0.78	3.13	1.56
17d	CH_3	Cl	7.1 ± 0.6	3 ± 1.0	1.25	6.25	2.5
17e	CH_2CH_3	Br	3.8 ± 0.4	1 ± 0.5	1.03	6.25	2.78

Table 6 gives the Ki values for those molecules as *C. albicans* AHAS antagonists. All remaining compounds are with minimal inhibiting properties on that enzyme, although 17a, 17c and 17e are strong *C. albicans* AHAS antagonists with Ki values in the 3–4 nM range, roughly twice as strong as those found for CE. Fig. 18 shows a visualization of the antagonistic activities data for 17a. With a halogen bonded to both moieties the X and R, derivatives exhibit a decreased binding activity for *C. albicans* AHAS (26−1199 nM). The *C. albicans* AHAS binding activity is marginally reduced when a hydroxyl group is added to R (Ki values of 15–27 nM). Therefore, when simply a methyl group is connected at this site, the hydrophobic effect cannot be countered by the new hydrogen bond that is formed. Unsurprisingly, with this large group connected, compound exhibited no inhibitory effect for *C. albicans* AHAS. However, with Ki values of 49.8 and 13.0 nM, respectively, where X is

Br or I in place of Cl are effective antagonists. This implies that it would be feasible to cause conformational modifications to make room for this large group on the attachment site of herbicide here, provided that the heterocyclic ring is securely bound. On the other hand, those moieties attach to *C. albicans* AHAS as yet uncharacterized manner. Of them, 17a-17e were the most effective, with MIC90 values ranging from 0.72 to 2.0 μg/mL (Table 6). In the tests, drugs with Ki values < 20 nM all showed good action, whereas those with values significantly higher than ~20 nM generally did not show any discernible suppression of *C. albicans*. Ethyl 2-(N-((4-iodo-6-methoxypyrimidin-2 yl)carbamoyl)sulfamoyl)benzoate (17a) is found to be the most effective of these substances, in cell-based tests, it has a MIC_{90} of 0.7 μg/mL for *Candida albicans* AHAS and a Ki value of 3.8 nM for this fungus.[14]

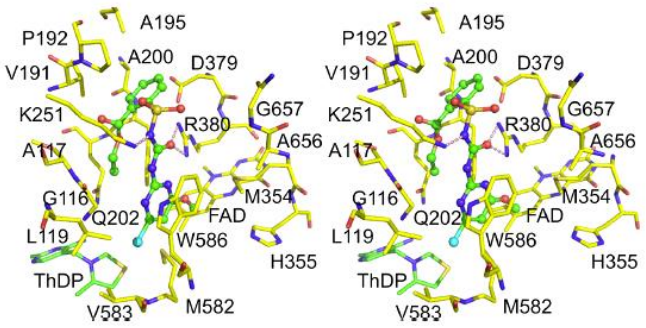


Fig. 18: Visualization of the antagonistic activities data for 17a.[14]

4.2 It was noted that substituted pyrimidine was a significant pharmacophore in antifungal drugs and increased focus has been placed on enhancing antifungal efficacy through pyrimidine ring structural modification. When it came to five fungal phytopathogens (*R. solanii, P. capsici, P. syringae, C. cassiicola*, and *B. cinerea*), compound 19a was more effective than the controls 25 mg/L. These findings suggest that SUs may be able to inhibit some phytopathogenic fungi and that an aryl group on a pyrimidine ring is advantageous for antifungal action. Table: 7 shows compounds 19b, 19c, 19d and 19e were more effective against two fungus than the controls. The compounds may be selective for the phytopathogens, as evidenced by the fact that *R. solanii* was more susceptible to the target compounds than the other fungi among all those examined. The following results are drawn from a comparison of compound 19 fungicidal activity against six tested fungi to those of controls: (1) An aryl group on the pyrimidine ring is advantageous for antifungal activity, as demonstrated by the title SUs with bulky substituted groups (aryl) in the pyrimidine moiety having clearly significantly higher

antifungal activities than Nicosulfuron (pyrimidine was substituted by methoxyl). (2) Of the aryl groups, the six-membered aromatic rings with electron-deficient groups and the five-membered aryl-hetero cycles showed much greater inhibitory activity than the others. Compound 19a (2-furyl), for instance, demonstrated much more fungicidal activity against the tested fungi than the others. (3) The inhibitory rate and the substitutents on the phenyl in the benzyl series do not directly correlate; nonetheless, it was shown that bromine was an essential component in boosting the fungicidal action. Compound 19e (p-bromophenyl) shown encouraging activity against three fungus, comparable to the control. (4) Furthermore, compared to compounds 19g and 19h (m- or p-nitrophenyl), the addition of pyridyl groups (19b and 19c) did not result in a discernible increase in activity against the tested fungi.

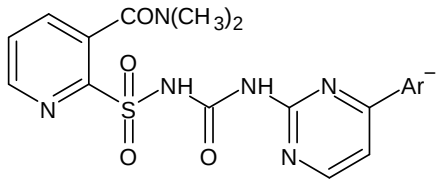


Fig. 19: Compound with antifungal activity.

Table 7: Sulfonylurea derivatives as antifungal agents.

Compound	Ar	Dosage ($mg\text{-}L^{-1}$)	R. solanii	P. syringae	P. capsici	C. cassiicola	B. cinerea	F. oxysporum
19a	2-furyl	100 25	81.7 60.4	43.9 25.5	67.6 36.2	62.0 53.4	70.0 46.6	38.4 19.2
19b	2-thienyl	100 25	84.1 65.9	38.2 21.3	32.7 14.4	39.6 25.7	30.6 24.9	32.9 18.1
19c	3-pyridyl	100 25	76.3 59.0	34.5 19.1	42.6 25.4	40.9 28.3	55.0 42.3	22.6 4.9
19d	4-chlorophenyl	100 25	79.0 60.2	46.2 26.5	57.9 27.1	39.6 27.4	62.6 36.4	54.4 34.7
19e	4-bromophenyl	100 25	63.3 44.1	24.5 5.1	75.3 41.5	72.7 62.5	50.4 31.4	22.6 11.1
Chloroethalonil	-	100 25	-	-	-	62.1 49.7	-	-

Herbicidal actions shows that the bulky group aryl added to the pyrimidine moiety is detrimental to herbicidal activities, as indicated by the fact that the majority of title compounds 19 exhibited incredibly low inhibitory activities against the tested plants. Leading compounds for the creation of new antifungal drugs were compounds 19a and 19e. The bulky groups on the pyrimidine ring were detrimental to herbicidal activity, according to the herbicidal data.[15]

4.3 Here, pharmacophore combination and bioisosterism strategies were used to design and synthesize three series of new sulfonylureas (SUs) that contain aromatic-substituted pyrimidines.

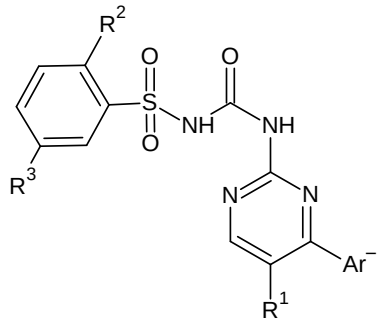


Fig. 20: Derivatives with fungal inhibiting properties.

This further demonstrated that carrying bulky groups such as aryl at the pyrimidine ring was essential to enhancing antifungal activity. Hetero cycles or substituents had a significant impact on SUs activity. Some SUs with a bulk group at the pyrimidine moiety showed moderate to good inhibitory rates against plant pathogenic fungi. Additionally found that certain sulfonylureas with an alkenyl moiety at the benzene ring had stronger antifungal properties than chlorsulfuron. Based on the lead compounds (Fig. 20) novel SU derivatives that were rationally designed and synthesized. Their antifungal activity was assessed *in vitro*. Using the comparative field analysis (CoMFA) paradigm, examined the structure-activity connections and determined the main structural elements that affect inhibitory activity. Furthermore, molecular docking was used to investigate 20a binding modalities with yeast AHAS and elucidate the title compounds possible antifungal mechanism. The presence of a significant green contour around the 4-methyl-phenyl group suggests that adding a bulky group here will boost the antifungal activity. The inhibitory activity of compounds (R^1 = Cl, Br, I) is higher than that of the other compound (R^1 = H). The electrostatic fields of CoMFA, the blue contour indicates an area where a drop in electron density is advantageous, while the red contour indicates the opposite. One distinguishing property is the presence of two large, activity promoting blue contours surrounding the 5-position of the pyrimidine ring and a large, medium-sized contour surrounding the 2-position of the benzene ring. The added groups shouldn't be overly electron deficient because there is also a minor red contour close to the pyrimidine rings substituents. Some compounds exhibit it; for example, 20b (R^1 = Br, R^2 = NO2), 20a (R^1 = Br, R^2 = Cl) and 20c (R^1 = Cl, R^2 = NO2) showed outstanding activity. According to 3D-QSAR analysis, the fungicidal activities might be enhanced by either an

electropositive group around the 4-position of the pyrimidine ring and the 2-position of the benzene ring or by a bulky group around the 5-position of the pyrimidine ring. The Cdocker is primarily maintained by a number of intermolecular interactions, such as hydrogen bonding, p–p stacking and vanderwaals interactions. 20a was autonomously docked into yeast AHAS. Docking consists of the yeast AHAS (PDB code: 1T9B) and 20a were used to create the flexible molecular docking model. The binding model is strikingly similar to yeast AHAS in complex with chlorsulfuron, as illustrated in Fig. 21. The aromatic ring is trapped in a pocket close to the proteins surface, and the 4-(2-furyl)-pyrimidine ring projects toward the active site when 20a is inserted into the hydrophobic tunnels entrance. According to the docking data, the negative Cdocker Energy was 13.85 kcal/mol and the negative Cdocker Interaction Energy was 32.04 kcal/mol. It primarily created two hydrogen bonds between the Arg 380 amino group and the oxygen atom of the sulfonyl group. It was indicated that aryl substituents are lucrative for antifungal activities and can properly embed within the active pocket. Their strong inhibitory effects are also largely owing to the p–p stacking interactions between 20a and the residues of Trp 586 and Val 583.[16]

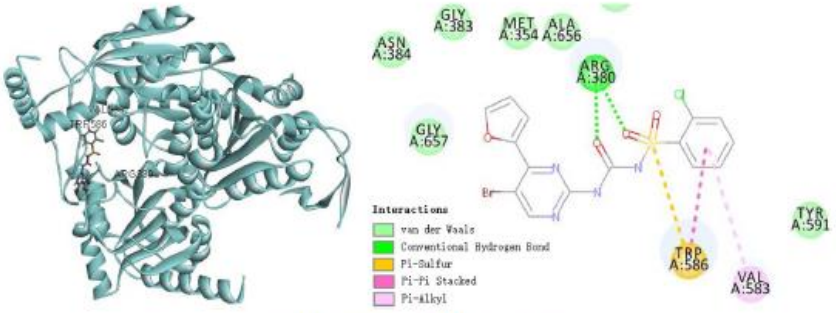


Fig. 21: Derivative 20a docking into yeast AHAS.[15]

5. Sulfonylureas on central nervous system

5.1 As anticonvulsant

For their anticonvulsant properties produced a more recent series of 1-(4-substitutedphenyl)-3-(4-((2,4-dioxothiazolidin-5-lidene)methyl)phenylsulfonyl)urea/thiourea(Fig. 22**)**. Similar to torasemide, which has sulfonylurea in its structure, the activity is characterized by its capacity to inhibit astrocytic Na+, 2HCl and K+ co-transport. Torasemide has neuroprotective properties, such as blocking the N-methyl-D-aspartate (NMDA) and non-NMDA receptors to assess antiepileptic activity and it blocks kainic acid-induced electrical discharges seen from the cortex. Effective anticonvulsant pharmacophore was demonstrated for the described drugs.[**Error! Bookmark not defined.**]

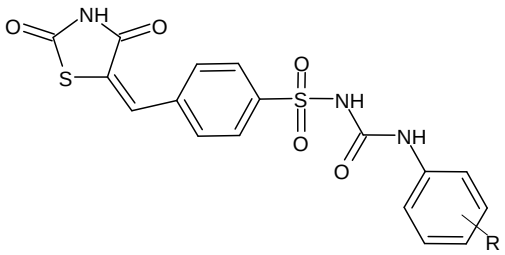


Fig. 22: Compound with anticonvulsant activity.

5.2 As anti alzeimers

The synthesis of harmful amyloid-β (Aβ), a key factor in Alzheimers disease, is started by the β-secretase enzyme, also referred to as β-site amyloid precursor protein cleaving enzyme 1 (BACE1). Because BACE1 plays a critical role in the production of Aβ, it is an essential therapeutic target for lowering cerebral Aβ concentrations in AD. Five fundamental structural characteristics of peroxisome proliferator activated receptor (PPARγ) agonists were shown to be necessary for their binding to PPARγ, according to research on their structure-activity connections. A hetero aromatic lipophilic tail, a linker and an acidic head are among its characteristics (Fig. 23). The linker is joined to an aromatic scaffold (spacer group). Accordingly, the sulfonylurea and sulfonamide moieties in that study operate as the acid heads necessary for PPARγ agonistic effect. In the compounds, the sulfonyl (SO2) group serves as a single atom that separates an aromatic group from an acid head. An aromatic spacer, such as a para-disubstituted phenyl group, is necessary for optimal PPARγ agonism. In the compounds, a variety of linkers have been used between the lipophilic tail and an aromatic spacer. These linkers are crucial for PPARγ agonistic function. In the end, different heteroaromatic nuclei were employed to provide the lipophilic tail required for PPARγ. The findings identified that the derivative (Fig. 24) demonstrated good activity on both targets; its EC50 values against PPARγ and BACE1 are 0.289µM and 1.24µM, respectively.[17]

Fig. 23: Structure-activity connections Sulfonylurea and Sulfonamide moieties.

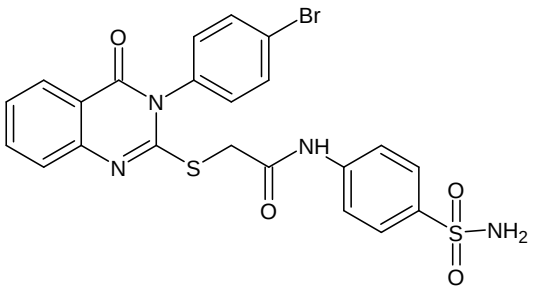


Fig. 24: Compound with anti alzeimers activity.

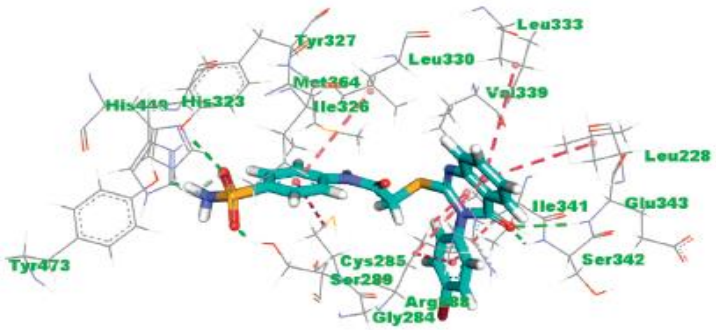


Fig. 25: 3D Docking structure of derivative (Fig. 24) into the active site of PPARγ[17]

6. Sulfonylureas as diuretic agents

6.1 One form of pyridine sulfonylurea loop diuretic is torasemide (rINN), sometimes known as torsemide (Fig. 26). Several mechanisms that function within the thick, medullary section of the ascending loop of henle can mediate the activities of torsemide. These include interference with the luminal surface Na+/K+/2Cl co-transporter, as well as anion exchange and the Na–K pump.[Error! Bookmark not defined.]

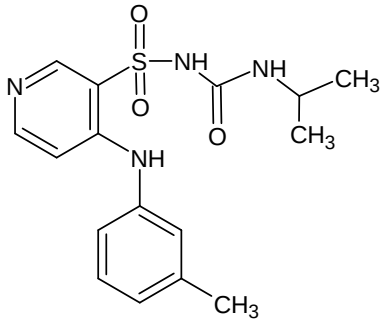


Fig. 26: Torasemide a pyridine sulfonylurea derivative.

6.2 As carbonic anhydrase (ca) inhibitors

A synthesis for nine aromatic/heterocyclic sulfonamides was devised. They are tested for the inhibition of three carbonic anhydrase (CA) isozymes. The new compounds showed good inhibition of all three CA isozymes, but an interesting discovery was that the ureas/thioureas

and particularly the compound mentioned (Fig. 27), had a higher affinity for the slow isozyme hCA I, which is generally less susceptible to sulfonamide inhibition than the rapid isozymes hCA II and bCA IV.[Error! Bookmark not defined.]

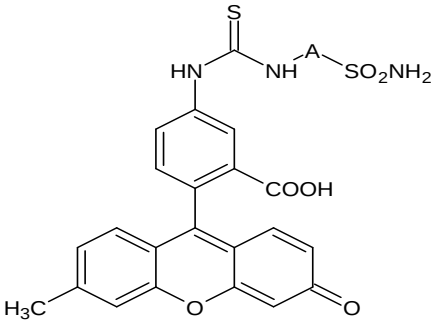


Fig. 27: Compound as carbonic anhydrase (ca) inhibitors.

6.2.2 From matching sulfonyl chlorides and amines, a new class of sulfonylurea derivatives was created. The sulfonylurea derivatives contain compounds (fig. 28, 29) with various attached moieties that interact significantly with human carbonic anhydrase II (CAII). When the sulfonylurea derivatives were evaluated *in vitro*, three molecules with excellent inhibitory action against CAII were found. The IC50 (109-137 μm) for CAII was shown by compounds with methyl (28a), isopropyl (29a), and o-tosyl (29b) moieties.

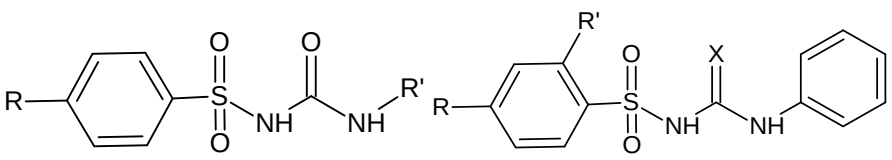
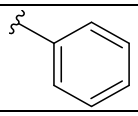
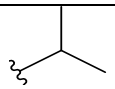


Fig. 28 **Fig. 29**

Fig. 28, 29: Sulfonylurea derivative as carbonic anhydrase.

Table 8: Sulfonylureas derivative 28a, 29a and 29b.

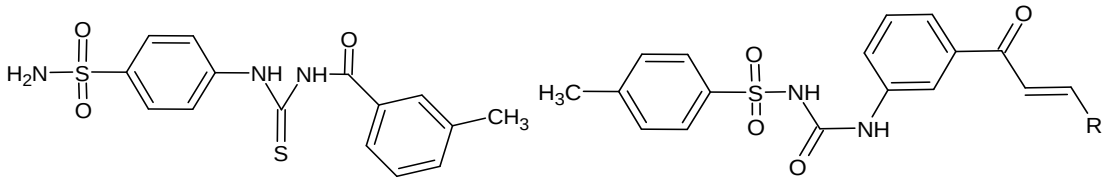
Compound	R	R1
28a	-CH3	
29a		-H
29b	-H	-CH3

Studies on fluorescence binding and cytotoxicity showed that these substances are non-toxic to cells and have a good binding affinity (18–34 μM) for CAII. Additionally 28a, 29a and 29b

molecular docking tests on CAII identified that those derivatives fit well on active region of CAII. At the two ends of the sulfonylurea moiety of each of these compounds are phenyl rings with different alkyl substitutions. The most significant inhibition of CAII was caused by the combination of methyl and phenyl (28a), 4-isopropyl and phenyl (29a) and o-methyl and phenyl group (29b) among the molecules with phenyl rings at the terminal ends of sulfonylurea. Compound 28a had an IC50 of 137.41 μm, compound 29a had an IC50 of 109.34 μm and compound 29b had an IC50 of 125.62 μm. Compounds 29a (34.20 μM) and 29b (18.57 μM) have relatively higher binding affinities than compound 28a (19.21 μM) for CAII. The biological examination of these compounds specifically shows that compounds 28a, 29a and 29b have good inhibitory efficacy. Additionally, it was shown that these substances have a high binding affinity for CAII.[18]

7. Sulfonylureas as 5-lipoxygenase (5-lox) inhibitors

A series of 3-aroyl-1-(4-sulfamoylphenyl) thiourea derivatives with a sulfonamide moiety were created as inhibitors of 5-lipoxygenase (5-LOX) (fig. 30). The IC50 value of 3-methyl benzoyl derivative, the most powerful molecule is 1.8 μM. Compared to quercetin, the reported compound has ten times the potency. It interesting to note that, according to the ferric reducing antioxidant power (FRAP) assay, it also exhibited the highest antioxidant activity. By using the Claisen-Schmidt condensation technique, a number of novel diaryl sulfonyl urea-chalcone hybrids was created. The potato 5-lipoxygenase enzyme was used to assess the *in vitro* 5-lipoxygenase inhibitory activity of each produced chemical. At IC50 levels, the evaluated drugs demonstrated a notable level of inhibitory action.[**Error! Bookmark not defined.**]



30a **30b**

Fig. 30: Derivatives of 5-lipoxygenase.

8. Sulfonylureas as antimicrobial agents

8.1 Nine of the twenty-one novel sulfonylurea derivatives (fig.31) that were designed and synthesized, showed inhibitory potencies against Gram-positive bacterial strains, including *Bacillus subtilis* ATCC 6633, vancomycin resistant *Enterococci*-309 (VRE-

309), *S. aureus* ATCC6538 and MRSA (Chaoyang clinical isolates). In particular, 32a and 32b showed inhibiting properties against the 4 strains of bacteria with MICs ranging from 0.78 to 1.56g/mL, outperforming the positive group methicillin (MIC of >200g/mL) and vancomycin (MIC of 1g/mL), as well as a number of other clinical strains of MRSA. Furthermore, every synthetic compound minimum inhibitory concentration (MIC) against *C. albicans* was higher than 100g/mL and *Candida* inhibiting actions of sulfonylureas is due to the inhibition of AHAS.

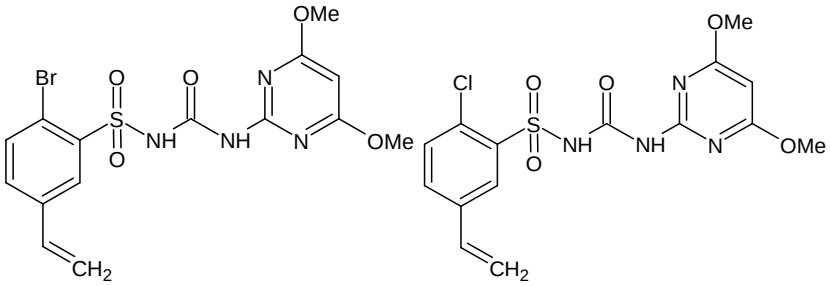


Fig. 31: Derivative-A and B as antimicrobial.

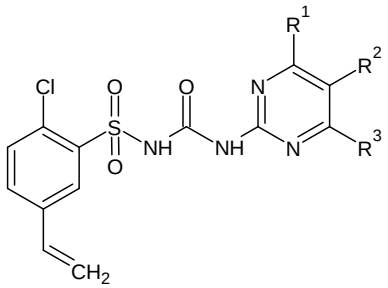


Fig. 32: Compounds showing inhibiting properties against the bacteria.

Table 9: The compounds with substantial activity.

	R^1	R^2	R^3	MRSA	*S. aureus*	VRE-309	*B. subtilis*	*C. albicans*
32a	Me	H	4-Br-Ph	0.78	0.78	1.56	1.56	>100
32b	H	H	2-thienyl	0.78	0.78	1.56	0.78	>100
32c	H	H	4-OMe-Ph	6.25	6.25	25	6.25	>100
32d	H	H	4-Cl-Ph	12.25	6.25	12.25	12.25	>100
Vancomycin				1.00	1.00	>16	0.5-1.00	ND
Methicillin				>200	3.13	ND	ND	ND
ND= Not determined								

Derivative-A (Fig. 31) found to exhibit *in vitro Ceratobasidiumcornigerum* inhibitions at a level compared to chlorothalonil with EC50 values of 4.54g/mL and 4.45g/mL, respectively. Derivative-B demonstrated significantly greater *in vitro Candida albicans* SC5314 inhibiting properties (MIC of <0.05g/mL) compared to fluconazole, an antifungal medication (MIC of

1.56g/mL). The bromide group present in the derivative A was substituted with chlorine to form a molecule. However, Derivative-B bioactivity against *S. aureus* ATCC6538 was extremely weak (MIC of >40g/mL). 21 target derivatives with phenyl-5-vinyl and pyrimidinyl-4-aryl groups are created and manufactured in an attempt to find new antibiotics to fight bacterial resistance. The MRSA inhibiting properties of 32a, 32b, 32c and 32d are furthermore investigated in contrary to a number of MRSA strains in order to confirm whether the active compounds have a broad antibacterial range. Table 9 summarizes that the compounds with substantial activity are also very effective antagonists to the remaining strains of MRSA. The compounds described in that work had the following substituted groups in their heterocycle rings: -SCH3, -CH3, and -OCH3. In contrast, the pyrimidine ring in the earlier study had an aromatic cycle or a aromatic system with substitution linked to it. By altering the substituents in the pyrimidine ring, sulfonylurea derivatives can be selectively inhibited against bacteria or fungi. MRSA (Chaoyang) inhibition was significantly impacted by R1 and R2, even though the R3 group was the main variable for the target compounds in this case. For instance, the R1 groups (-H, -CH3 and -OCH3) were the only differences between 32e, 32a and 32f. 32a had the lowest MIC and 32f exhibited no test activity.[19]

8.2 Summary of the new class of chemicals known as 15-membered azalides, which led to the discovery of novel sulfonylureas, ureas and thioureas as well as their antibacterial activity against several important erythromycin resistant organisms. A correctly attached aryl/hetero aryl carbamoyl group for enhanced activity against MLSB resistance and cleavage of the cladinose sugar and ketolide backbone for enhanced potency and activity against efflux resistance were among the structural characteristics that influenced the design of innovative macrolides. The inclusion of an unsaturated unit, namely a carbamoyl group, on nitrogen at position was anticipated to cause a major alteration in the steric environment and electrical characteristics in the macrolide upper part. It will also serve as an effective linker for the attachment of various groups permitting preparation of a library of compounds with the purpose of identifying novel bacterial inhibitors. When compared to azithromycin (MIC 8 μg/ml) and starting amine (MIC 16 μg/ml), compounds with methyl groups and chlorine in p-positions 33b (MIC 1 μg/ml), 33d (MIC 1 μg/ml), o-positions 33c (MIC 0.5 μg/ml), 33e (MIC 2 μg/ml) and fluorine in p-position 33f (MIC 2 μg/ml) demonstrated significantly improved activity against iMLS resistant *S. pyogenes* strain. Additionally, these compounds demonstrated comparable action to compound with MIC <0,125 μg/ml and superior activity with MIC 0.25 μg/ml against sensitive *S.*

pneumonia at two levels of dilution. But compared to both compounds, the activity against gram-negative bacteria were all lower. In Table 10 by adding a propyl linker and an extra cyano ethyl side chain, the antibacterial activity of the novel aryl sulfonyl carbamoyl derivatives fig. 33a-f, 34a-f and 35a-f against all tested erythromycin susceptible (*Ery-S*) Gram-positive strains was found to decrease in the series 33a-f > 34a-f > 35a-f. In conclusion, the antibacterial activity of novel azalides has been shown to improve when an aryl sulfonyl and benzene sulfonamido moiety is coupled to the position of a 15-membered azalide scaffold via a carbamoyl linker. Therefore, when compared to azithromycin, freshly synthesized sulfonyl ureas of azalides 33b–f showed noticeably better effectiveness against inducible resistant *S. pyogenes* strains. Sulfonyl carbamoyl derivatives 33, 34 and 35 showed a decrease in activity when the sulfonyl carbamoyl moiety moved farther away from the azalide ring.[20]

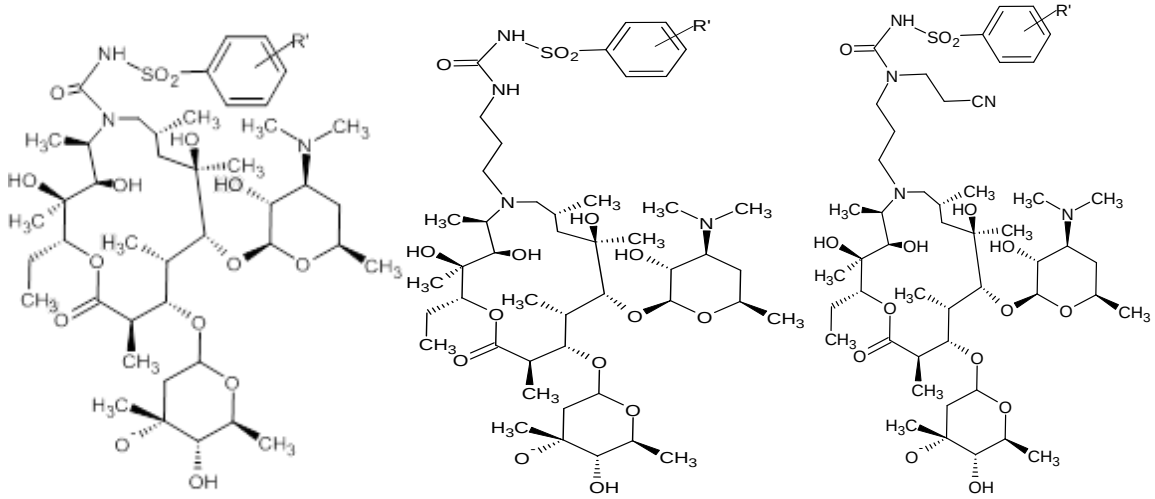


Fig. 33 (a-f) **Fig. 34 (a-f)** **Fig. 35 (a-f).**

Fig. 33,34,35: Sulfonylurea derivative as antibacterial activity.

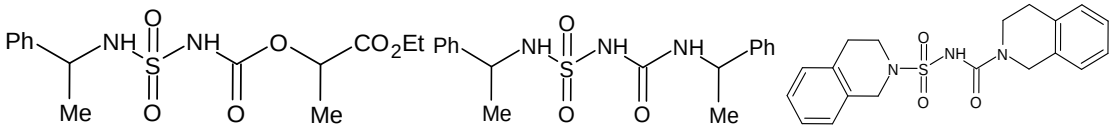
Table 10: The antibacterial activity of the novel aryl sulfonyl carbamoyl derivatives.

Compound	R′
a	H
b	p-Me
c	o-Me
d	p-Cl
e	o-Cl
f	p-F

8.3 As antibacterial agents

To find the minimum inhibitory concentration (MIC), the antibacterial properties of many derivatives of sufonylureas Fig. 36(a-c) were tested against clinical strains that were isolated.

The purpose was to compare the activity of the newly synthesized compounds with that of a control antibiotic, sulfonamide SSS. The strains utilized in the antibacterial activity tests were sensitive to varying quantities of molecules Fig. 36(a-c), according to the earlier study. Three compounds were found to have a strong effect against *Pseudomonas aeruginosa* and *Acinetobacterbaumanii* with a very high sensitivity (1, 2, and 0.5µg mL^{-1}).[21]



a **b** **c**

Fig. 36 (a-c) Derivatives of sulfonylureas as antibacterial.

9. Sulfonylureas as antihistamines

Prior researchers added sulfonylurea moiety to the molecules in order to provide anti-diabetic and KATP channel antagonism. Both aromatic (phenyl, 2,5-dichlorophenyl, and 4-trifluoromethylphenyl) and aliphatic (isopropyl and cyclohexyl) substituents were present. A number of sulfonamide derivatives were also produced at the same time, serving as the building blocks for the sulfonylurea molecules. The data on these drugs *in vitro* H3 receptor binding is compiled in Table 11

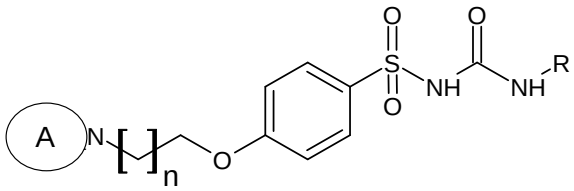


Fig. 37: Sulfonylurea derivative as antihistamines.

Table 11: Effective sulfonylureas among all the aromatic derivatives.

Compound	n	A	R	H3R IC50 (µM) ± SEM	hERG IC50 (µM)
37a	2	Pyrrolidine	Phenyl	0.164 ± 0.24	N.T.
37b	2	Piperidine	Phenyl	0.83 ± 0.004	$>10^2$
37c	2	Piperidine	4-trifluoromethylphenyl	1.74 ± 0.08	$>10^2$
37d	2	Pyrrolidine	1-naphthyl	0.08	$>10^2$

As shown by entries against 37a compound having an aromatic moiety for R often had lower IC50 values than the aliphatic substituents. Compounds 37a (0.16 M) and 37b (0.83 M) were the most effective sulfonylureas among all the aromatic derivatives that were examined. The

H3 affinity increased when a propoxy chain linker was added between the core ring and the basic amine (piperidine and pyrrolidine) (compounds 37a and 37b). A considerable loss of affinity was seen when the chain linker was either lengthened or shortened. A significant decrease in affinity was seen when an ethoxy carbonyl group was added to the cyclic amine. Compounds 37a and 37b showed comparable H3 affinity when either pyrrolidine or piperidine was used as the basic amine on the western portion of the molecule. When compared to their ortho- and meta-substituted counterparts, substances with a para-substituted phenyl group in R often exhibited a higher affinity for the human histamine H3 receptor. Compound 37c, the 4 trifluoromethyl phenyl counterpart, exhibited a potency that was 6–12 times greater than that of compounds with 10.40 M and 20.90 M. Compound 37d, substituted with a 1-naphthyl group, was the most potent sulfonylurea for the H3 receptor with an IC50 = 0.08 μM.[22]

CONCLUSION

Originally created to treat diabetes, sulfonylurea derivatives have a variety of biological actions, such as anti-inflammatory, anti-fungal, anti-microbial, anti-cancer and antimalarial properties. Their potency, specificity and therapeutic uses are greatly impacted by structural alterations. Developments in synthesis and SAR research have made it possible to create compounds that are more effective and have fewer adverse effects. These substances work via a number of pathways, including the stimulation of insulin secretion, the inhibition of enzymes, and the modification of cellular signalling. Due to their plasticity in pharmacology, sulfonylurea derivatives have great potential for treating both non-diabetic and diabetic diseases. In order to increase their clinical applications, future research should concentrate on minimising side effects, enhancing structures for target-specific activities and investigating novel therapeutic areas. Sulfonylurea derivatives have evolved beyond their traditional role as hypoglycemic agents and now exhibit a broad spectrum of biological activities. Their ability to regulate insulin secretion via pancreatic β-cell receptors has made them crucial in diabetes treatment. Structural modifications across different generations of sulfonylureas have enhanced their potency and reduced drug interactions, making them more effective in clinical applications. Beyond diabetes, sulfonylureas have shown promising anticancer properties by inhibiting ectonucleotidases, enhancing chemosensitivity, and blocking VEGFR-2, thereby suppressing tumor angiogenesis and proliferation. Additionally, they inhibit ABC transporters, which enhances the effectiveness of chemotherapy drugs. Their antibacterial, antifungal, and antitubercular properties have been explored, with certain sulfonylurea

derivatives exhibiting strong inhibition against *Mycobacterium tuberculosis* and *Candida albicans*, demonstrating potential as novel antimicrobial agents. Sulfonylureas have also been studied as antimalarial agents, where specific derivatives have inhibited *Plasmodium falciparum* growth and hemoglobin hydrolysis. Furthermore, sulfonylurea derivatives have been investigated for their anti-inflammatory properties by inhibiting 5-lipoxygenase, as well as their potential as carbonic anhydrase inhibitors, which could lead to new treatments for glaucoma and epilepsy. In the central nervous system, sulfonylurea receptors play a crucial role in modulating ion channels, making them potential targets for anticonvulsant and neuroprotective therapies, including Alzheimer's disease treatment. Their diuretic effects, particularly with derivatives like torasemide, have provided alternative treatment options for hypertension and cardiovascular diseases. Structural modifications of sulfonylureas have also contributed to better pharmacokinetic profiles, ensuring higher efficacy with reduced side effects. Overall, sulfonylurea derivatives represent a highly versatile class of compounds with wide-ranging pharmacological applications. Their structure-activity relationships continue to be an area of interest for developing more potent and selective therapeutic agents. Future research should focus on optimizing their molecular frameworks to enhance efficacy while minimizing adverse effects, paving the way for innovative drug development.

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