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"BEYOND SULFA: A DEEP DIVE INTO THE MOLECULAR VERSATILITY OF SULPHONAMIDES"

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ABSTRACT

Sulphonamides, known as a group of synthetic antibiotics, have allowed for the development of present-day chemotherapy for 100 years. While sulphonamides have been classified traditionally as antibiotics (the word is considered a 'shared' prefix), they have been demonstrated to have non-antibacterial uses as well, with a wide spectrum of pharmacologic actions including, anti-inflammatory properties, diuretic activity, antidiabetic effects, anticonvulsants, antitumor effects and carbonic anhydrase inhibitors. Therefore, a thorough pharmacologic assessment of sulphonamide derivatives can delineate their use as medications and potential candidates for drug repurposing relevant to not only antibiotics but also other drug classes or indications. We will focus on recent advances in medicinal chemistry that will encourage one to surge a number of sulphonamide-based compounds with newly designed structures with suitable pharmacologic activities and selectivity. A presentation on pharmacokinetics and mechanisms of resistance, distinctions on accidental ingestion, and toxicity issues as they relate to their use. Ultimately, the hopeful nature of the classical sulphonamides, as well as the newer versions, urge a broader view worth considering reinforcing the relevance of this class of medicines for contemporary drug development. A comparison between the periods 2015-2025 and 2000-2014 have been performed and presented for better understanding of versatility in use of sulphonamides for treatment of ailments other than microbial infections which were the only use presumed formerly.

KEYWOREDS: Sulphonamides, Pharmacological profile, anti – microbials.

INTRODUCTION

Sulphonamides, the first effective systemic antibacterial agents, have been important in medicine since their discovery in the 1930s. In the last decade (2015–2025), these compounds have been studied extensively, broadening their use beyond just antibacterial action to include a range of biological targets and disease conditions.

Even with the rise of bacterial resistance, sulphonamides still generate interest in the scientific community. Their flexible chemical structure, ease of making, and ability to serve as pharmacophores in drug design make them appealing. Recent progress in medicinal chemistry, molecular docking, and computational biology has led to renewed research on sulphonamides. This has resulted in new derivatives that show potential in treating cancer, inflammation, diabetes, malaria, and as carbonic anhydrase inhibitors.

This review aims to outline the pharmacological landscape of sulphonamides from 2015 to 2025. It highlights new mechanisms of action, structure-activity relationships (SAR), and their therapeutic potential. It also explores current methods for improving effectiveness while reducing toxicity, resistance, and unintended effects. By looking at recent literature and clinical trials, this paper offers an updated view on the changing role of sulphonamides in drug discovery and precision medicine.

Literature survey

The survey done for the study of uses and applications of sulphonamides in treatment of various diseases was divided to two time periods – Traditional Era (2000 to 2014) & Advanced era (2015 – 2025). Studies reported in advanced era (2015 – 2025).

- **Akış, Çakmak & Şentürk et al[1]: This study** discussed pyrazolone–sulfonamide hybrids as possible multi-target treatments, emphasizing the inhibition of cholinesterase and carbonic anhydrase. Highlighted their broad-spectrum potential by including molecular docking, in silico ADME/T profiling, and enzyme inhibition tests for CA isoforms and AChE/BChE.

- **ŞühedaÖzkul, EkremTunca, SametMert et al[2]:** The objective of the study was to create new pyrazole-3,4-dicarboxamide derivatives with sulfonamide groups and assess their ability to inhibit carbonic anhydrase (CA), specifically the human cytosolic isoenzymes hCA I (physiology's modest importance) hCA II (important target in hypoxia associated with cancer, epilepsy, and glaucoma) The researchers started by reacting pyrazole-3,4-dicarboxylic acid chloride with different amines and moieties that included sulfonamide. affinity for zinc (via the sulfonamide group). preference for CA isoforms. Drug-like appearance. 7a to 7i were the labels assigned to the last group of chemicals. Using ^{1}H-NMR and ^{1}C-NMR, structural characterisation was completed. Infrared Fourier-transform spectroscopy, or FTIR. Mass spectrometry with high resolution (HRMS). The substances have a high binding affinity for the zinc ion at the hCA II active site and are competitive inhibitors of CA.

- **Vawhal et al[3]:** This study is about cowmarin linked sulphonamides which inhibit DPP-IV. The researchers' objectives were to create novel hybrid molecules by joining two pieces of bioactivity. A well-known pharmacophore with anti-inflammatory and antioxidant qualities is coumarin. Sulfonamide is a common and adaptable pharmacophore in medicinal chemistry. Analyze ADME characteristics, toxicity, and binding interactions with computational methods, and assess their capacity to inhibit DPP-IV. In order to boost enzyme-binding affinity through dual functionality, the scientists chemically linked coumarin cores with sulfonamide units to create 22 derivatives (designated 6a to 6v). Molecular hybridization, which combines two pharmacophores into a single molecule to more efficiently target the DPP-IV active site, was used to develop the compounds. In Vitro Inhibition of Enzymes Assay Method: A fluorometric approach to quantify the DPP-IV enzyme activity inhibition.

Sitagliptin, a well-known DPP-IV inhibitor, was employed as a reference medication for comparison ($IC_{50} \approx 0.018$ µM).

- **Elmongy et al[4]:** This study focused on thienopyrimidine –sulfonamides hybrids effect on antibacterial /antifungal activity. The core of a thienopyrimidinehybridized with different sulfonamide parts. The targets were identified through in-silico docking, antibacterial dihydrofolate reductase (DHFR) is identified. For the production of ergosterol, antifungal squalene epoxidase is necessary. Docking data show robust and accurate fits, with binding conformations having an RMSD ≤ 1.9 Å. Compounds 8iii, a top antifungal, and 12ii, a top antibacterial, had the highest binding energies. agar well diffusion and MIC measurement against two species of Candida and six bacteria, including Staphylococcus aureus and E. coli. At position 3, cyclohexathienopyrimidine is coupled with sulfadiazine to form compound 12ii. Shown the highest level of antibacterial activity, which is in line with high DHFR docking scores. Compound 8iii: The highest docking affinity to squalene epoxidase and the strongest antifungal effectiveness against Candida strains were demonstrated. The results of ADMET and physicochemical tests showed, high tolerance for cellular membranes, oral bioavailability is projected to be moderate to low, suggesting potential difficulties with absorption. All hybrids, however, met drug-like property standards (such as Lipinski's rule), with compound 4i having the highest drug-likeness index score at about 1.58.

- **Mohammadi-Khanaposhtani et al[5]:** This report studied about the synthesis of eight new hybrids which is constructed by combining sulfonamides with 1,2,3-triazole. Using the CuAAC ("click" reaction), which attaches a sulfonamide moiety to a terminal alkyne-bearing precursor and reacts with different azides to make 1,4-disubstituted 1,2,3-triazoles, the eight hybrids were created. It was also tested against A549 cells from human lung cancer. Compounds 9d and 9g demonstrated superior cytotoxicity in the same experimental circumstances, with IC_{50} values in the range of ~3.8–4.3 µM, which is noticeably more effective than cisplatin (~6.2 µM).

- **Irfan et al.[6]:** This study explains about quinoxaline derivatives to create the quinoxaline core, o-phenylenediamine condenses with 1,2-dicarbonyl molecules. Further processes involving sulfonation or sulfonamide coupling by application of solvent-free synthesis, microwave-assisted synthesis, and environmentally friendly reagents. Quinoxaline-sulfonamide hybrids exhibit promise for a variety of biological targets like g ram-positive and gram-negative pathogens are effectively combatted by antibacterial and antifungal agents. It stop kinase pathways and trigger apoptosis as antitumor measures. Effective against targets linked to HIV and influenza, reduce inflammation and scavenge free radicals via modifying the expression of cytokines.

- **Branowska et al[7]** report in Molecules on the production of new 1,2,4-triazine sulphonamides via sulfenamide intermediates. These substances' structural characteristics and anticancer potential were assessed. A number of compounds showed encouraging cytotoxic effects on specific cancer cell types. Strong binding affinities to cancer-related targets were found by molecular docking experiments, confirming their promise as anticancer drugs. According to the study, 1,2,4-triazine sulphonamides show promise as scaffolding for future advancements in cancer treatments.

- **Lolak et al.[8]** present the synthesis and pharmacological evaluation of sulphonamides containing 1,3,5-triazine motifs in their paper published in the Journal of Enzyme Inhibition and Medical Chemistry. These substances' antioxidant qualities and inhibitory effects on acetylcholinesterase, butyrylcholinesterase, and tyrosinase—enzymes connected to pigment-related and neurological diseases—were examined. Numerous compounds demonstrated substantial antioxidant capacity and notable multi-target activity. According to the results, these triazine-based sulphonamides show promise as neuroprotective and dermatological therapeutic agents that could be developed further.

- **Durgun et al:[9]** created eight Schiff base derivatives based on sulphonamides. FT-IR, NMR (^1H & ^13C), LC-MS, and elemental analysis were used to characterize the compounds. Acetylcholinesterase (AChE) and carbonic anhydrase I & II (CA I/II) were pharmacologically examined for enzyme inhibition; their Ki values, which range from 10 to 100 nM, demonstrated strong action. ABTS, DPPH, CUPRAC, and FRAP tests were used to measure antioxidant capacity; compounds containing amines demonstrated about 70% radical scavenging activity. Their ability to bind enzymes was validated by in silico docking, which also demonstrated their relevance in the medication design process for neurodegenerative diseases.

- **Vangala et al:[10]** used molecular dynamics, docking, and pharmacophore modeling to create sulphonamide derivatives that target the HIV-1 gp120 envelope protein. These chemicals were synthesized and tested experimentally. showed encouraging bioactivity data and a promising affinity in silico. Highlights of pharmacology: logical design against a viral target (gp120) verified using both lab-based and computational techniques.

- **Mishra et al[11]** created two series of derivatives of benzenesulfonamide that are strong inhibitors of human carbonic anhydrase (hCA), especially of isoforms II and VII. IC_{50} values that are low and indicate a high level of enzyme inhibition. Compounds demonstrated anticonvulsant efficacy in animal models (MES and scPTZ seizure models), as well as low toxicity and potential oral absorption.

- **Yousef et al[12]** A thorough analysis of pharmacokinetics and pharmacodynamics that differentiates between sulfonamides that are antibacterial and those that are not. examined ADME properties, examined SAR patterns, and identified problems with sulfa cross-allergenicity. gives fundamental information that will help in future drug development. [2018]

- **Patel et al[13]** created the diaryl ether aryl sulfonamide PF-05089771, which selectively blocks the $Na_V1.7$ sodium channel, a crucial target for pain signals. surpassed other sodium channel subtypes in potency and selectivity, moving closer to being a clinical candidate.

- **Arancha Pérez García:[14]** discovered aryl sulfonamides that possess potent anti-Mycobacterium tuberculosis properties. According to structure-activity studies, potency was increased by electron-withdrawing groups. Molecular docking indicated that DHPS and other folate pathway enzymes were inhibited. The compounds demonstrated oral drug-like qualities, low toxicity, and acceptable metabolic stability. These results demonstrate that aryl sulfonamides are promising candidates for creating novel therapies to combat drug-resistant tuberculosis.

- **Leeza, S. Zaidi, et al[15]** created and produced new hybrid compounds by joining a sulphonamide-piperazine moiety with a thienopyrimidine scaffold that targets the enzyme dihydrofolate reductase, or DHFR. Activity against: Plasmodium falciparum (K1 strain resistant to pyrimethamine and chloroquine) Entamoeba histolytica (strain HM1:1MSS) In molecular docking studies, a few compounds demonstrated good binding and superior antimalarial activity compared to conventional medications. showed minimal cytotoxicity in cell lines of Chinese hamsters. Strong binding to PfDHFR was confirmed by molecular docking, indicating their potential as potent antiprotozoal drugs.

- **Anusha et al[16]** describe the design, synthesis, and biological evaluation of new enantiomerically pure sulphonamide derivatives as potential antimalarial medicines. These chemicals showed strong in vitro action against Plasmodium falciparum strains, including drug-resistant variants. N-myristoyltransferase was proposed as a probable target by structural investigations and computer modeling. By combining stereochemical specificity with encouraging biological efficacy, the work demonstrates the promise of sulphonamide scaffolds in malaria medication discovery and lays the groundwork for future antimalarial drug research.

Remark on findings in advanced era

Over the decade from 2015 to 2025, sulphonamides have shown impressive versatility in their pharmacological uses. They have changed from traditional antibacterial agents to promising options for a variety of medical treatments. Progress in medicinal chemistry, molecular modelling, and high-throughput screening has made it possible to discover sulphonamide derivatives with strong anticancer, antidiabetic, antimalarial, anti-inflammatory, and enzyme-inhibiting effects.

Even with rising antimicrobial resistance, sulphonamides remain important structures in drug discovery because of their adjustable design and ability to target multiple pathways. Several studies during this time have emphasized the need to optimize the structure-activity relationship (SAR) to improve bioavailability, lower toxicity, and enhance selectivity toward new biological targets.

The findings from this decade highlight how relevant sulphonamides still are in modern drug therapy. Future research should aim at overcoming resistance mechanisms, developing directed drug delivery systems, and investigating their role in combination therapies. As personalized medicine progresses, sulphonamides are likely to continue being important in the quest for more effective and selective treatments.

Studies reported in traditional era (2000 - 2014)

Sulphonamides were once widely used as antibacterial agents. Between 2000 and 2014, their use was reevaluated due to rising antibiotic resistance and improvements in medicinal chemistry. Although their use as antimicrobials declined, interest in sulphonamides grew because of their potential for other therapeutic uses.

Researchers looked into sulphonamide derivatives for many treatments, including anticancer, antidiabetic, anti-inflammatory, antiglaucoma, and anticonvulsant effects. A major breakthrough emerged with their ability to inhibit carbonic anhydrase and modulate various enzymes like metalloproteinases and kinases.

The flexible structure of sulphonamides allowed for in-depth structure-activity relationship (SAR) studies and chemical changes, resulting in compounds with better selectivity and lower toxicity. Modern drug discovery methods, such as molecular modeling and high-throughput screening, helped identify new sulphonamide-based agents.

This review summarizes important pharmacological developments in sulphonamide research from 2000 to 2014. It highlights their shift from traditional antimicrobials to versatile platforms in modern drug development.

- **Sahoo, S. P. & Subudhi, B. B.[17]:** In this study by combining sulfanilamide with leucine, an important amino acid, a novel hybrid molecule was created, which was tested in rats utilizing in vitro H. pylori tests and ethanol-induced stomach ulcers. At 100 mg/kg, it produced 66.7% ulcer prevention in the ethanol model. Seven clinical strains of H. pylori showed growth inhibition (MIC 12.5–50 µg/mL). showed a good safety and toxicity profile. The medicinal chemistry approach makes use of two functions: the sulfonamide molecule offers antibacterial activity, while the amino acid supports mucosal protection. Ethanol-Induced gastrointestinal Ulcer Model (in Rats) Methodology: After inducing gastrointestinal mucosal injury in the rats with 100% ethanol, the hybrid compound (referred to as "Compound 5"), administered at doses of 25, 50, and 100 mg/kg, was administered. Results of Efficacy: The molecule provided 66.7 percent ulcer protection at 100 mg/kg, while the usual medication ranitidine only provided 45.1 percent protection at the same dosage A distinct dose-response was evident in the study: 16.7% protection at 25 mg/kg, 59% at 50 mg/kg, and 66.7 percent at 100 mg/kg. Measurements of the gastric ulcer index (ulcer length and petechial lesions) verified that Compound 5 considerably decreased mucosal damage. It significantly outperformed ranitidine, a popular H2-receptor blocker, in terms of ulcer protection at the highest dosage. The hybrid showed MIC values against seven clinical strains of H. pylori that ranged from 12.5 to 50 µg/mL. Given that the bacteria is a primary cause of chronic ulcers, the compound's bacteriostatic/bactericidal activity makes it a viable supplement or substitute for traditional H. pylori eradication treatments.Usually, ethanol causes ulcers by disrupting the mucosal barrier, causing inflammation and oxidative stress. The combination most likely improves mucosal defense by scavenging reactive oxygen species, increasing mucus secretion, and improving mucosal blood flow—functions shown with other amino acid-based anti-ulcer drugs. By blocking bacterial dihydropteroatesynthase, the sulfanilamide moiety prevents H. pylori from synthesizing folic acid and prevents bacterial growth and adhesion. This combination offers a promising multi-modal treatment approach against gastric ulcers by combining tissue protection with antibacterial activity, especially against H. pylori. Compound 5, a leucine–sulfanilamide hybrid, is a potentially effective dual-action anti-ulcer drug. It offers more protection than ranitidine against ethanol-induced stomach ulcers in rats. Its MICs range from 12.5 to 50 µg/mL, indicating focused antibacterial action against H. pylori. In evaluations of the liver and kidney, it shows a clear acute toxicity profile. Its dual treatment approach, which combines antibacterial activity with cytoprotection, targets two important pathways that lead to ulcers and may be superior to current mono-target drugs.

- **Patel, N. B., Purohit et.al[18]:** created benzothiazole-cored thiazolopyrimidine sulfonamides that have antibacterial and antitubercular properties. The researchers combined the following to form a hybrid structure, a thiazolopyrimidine ring, a bioactive tricyclic heterocycle a sulfonamide group with antibacterial properties (-SO_2-NH), a bioactive heterocycle with antibacterial and antitubercular properties is the benzothiazole moiety.

The thiazolopyrimidine scaffold should be built via cyclocondensation methods. The sulfonamide is installed at a crucial nitrogen by introducing sulfonyl chloride. The final products (labeled 5a–5j) are produced by linking the benzothiazole moiety, perhaps through amide/thiol chemistry or cross-coupling. Characterization: Using elemental analysis and spectroscopic techniques (^1H/^{13}C NMR, IR, MS), structures were verified. Tested against a variety of fungus strains as well as Gram-positive and Gram-negative bacteria. Ciprofloxacin and other antibiotics were standard reference medications. Numerous analogs showed substantial microbe inhibition with MIC values in the low µg/mL range. Demonstrated a broad-spectrum antibacterial profile by demonstrating effectiveness against fungal infections as well. Using the Microplate AlamarBlue Assay (MABA), anti-Mycobacterium tuberculosis was investigated. MICs for the compounds ranged from 1.6 to 12.5 µg/mL. the smallest MICs (1.6 µg/mL) were found in analogs 5b, 5d, and 5h (containing para-halogens including fluoro, bromo, and methyl), which were equivalent to first-line medications like isoniazid and ethambutol. bacterialdihydropteroate synthase DHPS), which prevents the production of folate. DprE1 and mycolic acid production enzymes are examples of potential TB targets that match docking findings in more recent benzothiazole anti-TB drugs. Though more mechanistic research is necessary, targets for thiazolopyrimidine systems may include respiratory enzymes (such as DNA gyrase). The work shows how molecular hybridization can be used to increase potency and spectrum by mixing many heterocyclic pharmacophores. These chemicals are novel leads with antitubercular efficacy comparable to that of conventional medications and promising antibacterial breadth.

- **Ovais et al.[19]:** This study investigated about the benzenesulfonamide-containing new 2-pyrazoline derivatives that exhibit anti-inflammatory and anti-hyperglycemic properties in vivo. The compounds are trisubstituted 2-pyrazolines, which are produced by condensing 4-hydrazinyl benzenesulfonamide with chalconeprecursors. By combining a benzenesulfonamide "tail" with the heterocyclic pyrazoline core—which has anti-inflammatory and metabolic properties—this design improves target binding and bioactivity. Carrageenan-induced edema and egg-white paw edema experiments in rats were used to assess the in vitro anti-inflammatory activity. At 300 minutes after induction, compounds (such as 6a, 7a, 9a, and 10a) decreased edema by approximately 28–30%, surpassing or exceeding celecoxib's effectiveness (~22.7%). Using celecoxib as a reference, molecular docking verified advantageous interactions with COX-2 active sites. inhibition of the inflammatory enzymes PLA_2 and COX2, which lowers the generation of cytokines and edema.S uppression of IL-1β, reduction of blood glucose, and metabolic modification through the insulin-signaling and glucose-processing pathways (ACE2/PI3K/AKT). Aldose reductase and α-glucosidase enzyme inhibition guards against hyperglycemia and diabetes consequences. By combining two pharmacophores, 2-pyrazoline benzenesulfonamides effectively reduce inflammation (either better than celecoxib or on par with it) and lower blood sugar levels through a variety of metabolic and enzyme routes. The close structural analogues clearly suggest the derivatives' potential as dual-function medications, particularly pertinent for treating inflammation associated with diabetes, even though in vivo glucose-lowering studies have not been reported for all of them.

- **Ning et al.[20]:** This study created a range of multipurpose neuroprotective drugs, known as (E)-3,4-dihydroxystyryl aralkylketone derivatives, that exhibit both neuroprotection in cellular models and potent antioxidant and anti-inflammatory properties. based on a catechol (3,4-dihydroxyphenyl) scaffold that is known to scavenge radicals and is connected to different aralkylketone or sulfone moieties by a styryl bridge. Several features are intended to be improved by this hybrid design: Antioxidant (ROS are scavenged by the catechol moiety), anti-inflammatory (controls the expression of iNOS and NO production), Blood-brain barrier (BBB) permeability-tuned molecular flexibility. Activity of antioxidants tested on PC12 cells that were subjected to ROS source $H2O_2$. At 2.5 µM, many derivatives demonstrated >90% cell viability. At that concentration, a remarkable molecule ("6.22) with a cyclopentyl-propyl chain brought viability back to 94.5%. anti-inflammatory properties using macrophages or microglia activated by LPS to produce NO. Compound 6.22's IC_{50} of 1.6 µM was significantly better than that of the lead compound ("1"), which had an IC_{50} of 13.4 µM. shown Anti-apoptotic activity even at low µM concentrations, Annexin V-FITC/PI tests in PC12 cells after $H2O_2$ damage demonstrated 6.22 significantly inhibited apoptosis, consistent with its ROS/NOS neutralization activity. In neurodegeneration (such as Parkinson's and Alzheimer's), oxidative stress, inflammation, and apoptosis interact in a complicated way. Multiple neurotoxic pathways are addressed simultaneously by combining antioxidant and anti-inflammatory mechanisms, which may result in more potent medicines than single-target medications.

- **JeanYves Winum et al.[21]:** The polypharmacology of sulfonamides includes the strong inhibition of many mammalian carbonic anhydrases by pazopanib, a multitargeted receptor tyrosine kinase inhibitor used in therapeutic settings. The term "polypharmacology" describes a drug's capacity to interact with more than one target. This may be advantageous or disadvantageous, advantageous if several targets work together to produce the intended treatment outcome. detrimental if side effects or toxicity are brought on by off-target effects. A class of chemicals known as sulfonamides has the functional group -SO_2NH_2. They are renowned for their involvement with, antimicrobial treatment, carbonic anhydrase (CA) enzyme inhibition. The reversible hydration of CO_2 is catalyzed by the zinc metalloenzyme family known as CAs.

$$CO2+H2O\leftrightarrow HCO3-+H+$$

Numerous physiological processes include them, such as, Control of pH,t ransport of CO_2, acidification of tumor microenvironment. Several CA isoforms, including CA I, II, IX, and XII, are overexpressed in cancer. A multitargetedtyrosine kinase inhibitor (TKI) licensed by the FDA, pazopanibis used to treat malignancies such as soft tissue sarcomas and renal cell carcinoma. It targets kinases such as c-Kit, PDGFR, and VEGFR. Carbonic Anhydrase Inhibition. Pazopanib strongly suppresses a number of human CA isoforms, including:

Both CA IX and CA XII are overexpressed in hypoxic malignancies and are linked to cancers. The sulfonamide group of pazopanib most likely inhibits CAs by binding to the zinc ion in the enzyme's active site, a recognized mechanism for sulfonamide-based CA inhibitors. CA IX and XII have a key role in tumor pH control. Their inhibition may, disrupt the tumor's acidic environment, stop the growth and spread of tumors. This suggests that pazopanib's anti-cancer effectiveness may result from a polypharmacological action that includes both kinase and CA inhibition. The drug pazopanib, which is intended to inhibit tyrosine kinases, also inhibits carbonic anhydrases, particularly those linked to the growth of tumors. This study is an excellent illustration of polypharmacology in action.

- **Syed Ovais et al.**[22]: In this study the researchers synthesized eight novel 2-pyrazoline derivatives (designated 2a–2h) were created by the researchers. They started with chalcones or flavanones and used a traditional cyclocondensation procedure to react them with 4-hydrazinobenzenesulfonamide hydrochloride. The pyrazoline core containing the benzenesulfonamidepharmacophore was obtained by refluxing the chalcone with the hydrazine derivative in ethanol. spectroscopic techniques was to characterize each derivative: NMR for ^{1}H and ^{13}C,, Mass spectrometry. Additionally, elemental analysis confirmed the chemical structures. The carrageenan-induced rat paw edema model, a gold standard for anti-inflammatory screening, was used for in vivo testing. Importantly, compounds 2c and 2e did not result in ulcers, indicating a safer gastrointestinal profile. They also demonstrated substantial edema inhibition that was comparable to the reference medication celecoxib. Mild inhibition was found in in vitro enzymatic experiments against the ovine COX-1 and COX-2 enzymes, suggesting that the anti-inflammatory mechanism may not be exclusively dependent on COX enzyme suppression. The study includes early anticancer screenings even though its main focus was anti-inflammatory,s ignificantantiproliferative action was demonstrated by compounds 2c and 2f across the NCI-60 tumor cell line panel. Specifically, 2f demonstrated low micromolar GI_{50} values against cell lines from non-small cell lung (EKVX), colon (COLO 205), and leukemia (MOLT4, SR). blood-glucose lowering action was studied in this topic, the main study describing these effects seems to be a different series that focuses on derivatives of benzenesulfonyl-thiourea that are specifically designed to be anti-hyperglycemic medicines.

That team used benzenesulfonamide–thiourea chemistry to create 17 analogues, which they then tested on hyperglycemic rats fed glucose. A few of them acted as aldose reductase inhibitors and had moderate to good antihyperglycemic effects. effectively presented new hybrids of 2-pyrazoline and benzenesulfonamide with, similar to celecoxib in terms of anti-inflammatory effectiveness, but maybe safer for the stomach. There are several substances that have broad anticancer potential.

- **Pacchiano et al.**[23]: In this study researchers investigated about ureido-substituted benzenesulfonamides that target carbonic anhydrase IX (CA-IX), a tumor-relatedisoform associated with hypoxia and metastasis, were designed, synthesized, and bioevaluated. 4 {[(3′nitrophenyl)carbamoyl]amino}benzenesulfonamide, a remarkable chemical, demonstrated strong enzymatic inhibition and inhibited metastasis in vivo. The compounds are made up of a flexible ureido (-NH-CO-NH-) bridge connecting a variety of aromatic "tail" groups to a benzenesulfonamide "warhead," a known zinc-binding fragment. In order to maximizeisoform selectivity between cytosolic (I/I) and tumor-associated (IX/XII) isoforms, library modifications concentrated on altering the tail substituents. In the active site of CAs, the Zn2+ is coordinated by the benzenesulfonamide group. Selectivity toward CA IX/XII over I/II is improved by the ureido linker's flexibility, which enables the tail to take advantage of varied residues at the enzyme entrance. This "gatekeeper region" binding mechanism is supported by X-ray evidence. These substances demonstrated low-nanomolar K□ values against CA IX and XII, with certain variations showing noticeably less inhibition (>400 nM) of CA I/II. Compound 25 in the follow-up work, SLC-0111, for instance, has K⊠≈45 nM for CA IX and ~4–5 nM for CA XII, while preserving cytosolic isoforms. Treatment with the nitro tail compound at 45 mg/kg significantly decreased the number of metastatic nodules in a mouse model utilizing aggressive 4T1 breast cancer cells, which are known to spread to the lung. After intravenous tumor cell injection, mice's metastasis was inhibited, as confirmed by follow-up investigations using related drugs like U-104. Under tumor hypoxia, CA IX/XII is elevated through HIF-1, resulting in an acidic milieu that encourages invasion and metastasis. Therefore, selective inhibition of these isoforms is a tactic to upset the pH balance of tumors, hinder invasive activity, and prevent the spread of metastatic disease. Clinical candidates like SLC-0111, which is currently undergoing Phase 1/2 studies for pancreatic cancer, were made possible by this class of drugs. The ureido moiety is still a crucial structural motif for balancing potency with isoform selectivity. Efficacy and pharmacological profiles are continuously improved by ongoing structural–activity relationship (SAR) research, particularly those including bis-ureido linkers (in subsequent works).

- **William J. Zuercher, Richard G. Buckholz,et al.**[24] In this investigation researchers discovered that **tertiary sulfonamides**, especially compounds like **GSK2033**, exhibit **potent LXR antagonism** with **cell-based activity**. This structural class offered:
    - **High affinity** for LXR ligand-binding domain (LBD)
    - **Antagonistic action** without inducing unwanted gene expression
    - Good **bioavailability** and **stability**

Tertiary sulfonamides were discovered as novel scaffolds through the use of medicinal chemistry techniques and high-throughput screening. GSK2033 is a lead chemical that was obtained through sulfonamide substitutions and side chain optimization. GSK2033 is a tertiary sulfonamide with three distinct groups ($R–SO_2–NR'R$) bound to the sulfonamide nitrogen. This special quality improves, Steric bulk, increasing the level of selectivity, The LXR binding pocket's hydrophobic interactions, Resistance to metabolic breakdown and hydrolysis. GSK2033 attaches itself to LXRα/β's ligand-binding domain (LBD). It stops the recruitment of coactivators, which is necessary for the transcription of genes. displaces natural or artificial agonists by acting as a competitive antagonist. efficiently inhibits LXR target genes, including, SREBP-1c and ABCA1 are implicated in lipogenesis and cholesterol export. GSK2033 and related substances may be utilized for, Treat liver disease that is not alcoholic fatty (NAFLD), Control the atherosclerosis, ameliorate inflammatory conditions without raising triglyceride production (a challenge for agonists).

- **Smits et al.**[25]**:** GSK2033 and related substances may be utilizedfor, mostly expressed in: H_4R is a G-protein coupled receptor (GPCR). Bone marrow, Eosinophils, Mast cells, Basophils. GSK2033 and related substances may be utilized for: Even in the absence of histamine, inverse agonists inhibit the H_4 receptor's basal activity. There may be therapeutic advantages to targeting H_4R in, having asthma, Dermatitis atopic, It is rheumatoid arthritis, Rhinitis due to allergies. GSK2033 and related substances may be utilized for the following are the results of the synthesis and QSAR-guided optimization of H_4R inverse agonists, including arylguanidines and sulfonamides, Extremely strong and specific substances, Outstanding profiles of inverse agonists, Excellent therapeutic potential for inflammatory, asthmatic, and allergy conditions, These results mark a significant advancement in the development of next-generation anti-inflammatory medications that target histamine signaling in ways other than H_1 and H_2 receptors.

- **Ferro S, Agnello S, and Gitto R,**[26] 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamides are synthesized and evaluated pharmacologically using organic synthesis techniques to produce novel sulfonamide derivatives and assess their potential biological activities, such as enzyme inhibition, antifungal, anticancer, and antibacterial properties.

The pharmacological properties of isoquinoline derivatives, particularly 1,2,3,4-tetrahydroisoquinolines (THIQs), include anti-inflammatory, anticancer, and antibacterial properties. The antibacterial and carbonic anhydrase-inhibiting qualities of sulfonamides are widely established. Strong bioactive compounds could result from combining sulfonamide and dihydroisoquinoline motifs in a single structure. 6,7-Dimethoxy-3,4-dihydroisoquinoline SynthesisBegin with homooveratrylamine, or 3,4-dimethoxyphenethylamine. Make use of the Pictet-Spengler response, react in an acidic environment with a ketone or aldehyde. forms a tetrahydroisoquinoline ring via cyclizing. At position 1 of the THIQ ring, an aryl group (such as phenyl or substituted phenyl) is added by the Grignard reaction or reductive amination. Arylsulfonyl chlorides, such as tosyl chloride and benzenesulfonyl chloride, react with the lactam (2-position NH) in the isoquinoline. Usually, a base (such as pyridine or triethylamine) is present when the reaction is occurring. 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamide is the final product. tested against cancer cell lines, including HeLa (cervical cancer) and MCF-7 (breast cancer). Cell viability is frequently evaluated using the MTT test.

tested against both fungal and bacterial species, including S. aureus and E. coli. The **synthesis of 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamides** offers a promising scaffold for developing **new bioactive molecules**. These derivatives have shown **notable anticancer and antimicrobial activities**, indicating their potential as lead compounds for drug development.

- **De Liguoro M. et al.**[27]**:** This study helps in Understanding the effects of veterinary antibiotics on the environment, especially in aquatic ecosystems, requires an evaluation of the toxicity of sulfamethazine (SMZ) on Daphnia magna, a crucial aquatic invertebrate used in ecotoxicology. This is a thorough description of the study's background, experimental setup, findings, and implications, particularly with regard to interactions between sulfamethazine and trimethoprim or other sulfonamides. A common veterinary sulfonamide antibiotic for use in poultry and cattle is sulfamethazine (SMZ). Following excretion, it reaches aquatic ecosystems by wastewater discharge, manure application, or agricultural runoff. Due to its sensitivity to contaminants, the freshwater crustacean Daphnia magna is frequently employed to evaluate environmental toxicity. It is used assess Sulfamethazine's acute and long-term toxicity to Daphnia magna. effects that are antagonistic, additive, or synergistic when SMZ is coupled with Sulfadiazine and sulfamethoxazole are examples of other sulfonamides. Sulfonamides are frequently taken with trimethoprim, a dihydrofolate reductase inhibitor.

For SMZ in Daphnia magna, sulfamethazine Alone EC_{50} (48 hr) is usually in the mg/L range (e.g., 50–200 mg/L), indicating moderate to medium acute toxicity. Reproductive production is impacted by chronic exposure, even at sub-lethal quantities (as low as µg/L).

- **Arshad M. N. et al.**[28]**:** This study aimed analyzing the structure–activity connections, hydrogen bonding, intermolecular interactions, and crystal packing behavior of sulfonamide compounds—which are frequently utilized in pharmaceuticals, particularly as antibacterial agents—were better understood thanks to these investigations. Using X-ray crystallography to investigate sulfonamide derivatives aims to, Find precise molecule structures in three dimensions, Examine intermolecular interactions, such as π–π stacking and hydrogen bonding, Recognize packing motifs, polymorphism, and tautomerism, Link structural characteristics to medication design and biological function. In 2009 crystallographic research on sulfonamide derivatives identified important structural characteristics that are necessary for, designing and optimizing drugs, recognizing biological activity, and enhancing the qualities of medicinal solids. The insights gained from these investigations served as a basis for further research on sulfonamide-based medicines.

- **Cheng, X.C., Wang, Q., Fang, H., Xu, W.F**[29]**:** This study provides a detailed study on the important role that sulfonamide functional groups play in the formulation and mode of action of inhibitors of matrix metalloproteinase (MMP). Based on the core, below is a breakdown and thorough explanation. The zinc-dependent endopeptidases are known as MMPs. They participate in physiological processes such tissue remodeling, wound healing, and angiogenesis and break down elements of the extracellular matrix (ECM).

MMP overactivity has been connected to cardiovascular illness, neurological diseases, arthritis, and cancer metastases.

To function, MMPs need a catalytic zinc ion (Zn2+) at their active site. In order to inactivate the enzyme, effective MMP inhibitors usually chelate this zinc ion, preventing substrate access.

Unlike hydroxamates, the most prevalent zinc-binding group in MMP inhibitors, sulfonamides do not directly bind to Zn^{2+}. Sulfonamides' NH group has the ability to interact with residues in the MMP active site via donating hydrogen bonds, this improves binding affinity and specificity.

Because of their amphipathic nature, sulfonamides help to optimize the solubility and bioavailability of inhibitors. This characteristic is particularly crucial for striking a balance between plasma half-life and cell permeability. A wide variety of conformationally flexible or rigid inhibitors are possible by including the sulfonamide moiety into either cyclic or acyclic scaffolds. Selectivity for particular MMP subtypes (such as MMP-2, MMP-9, etc.) is made possible by this. In contrast to previous inhibitors, especially hydroxamates, which exhibited broad-spectrum inhibition and off-target effects, sulfonamide-based MMP inhibitors exhibit decreased toxicity and enhanced selectivity. They have been investigated in neurological problems, inflammatory illnesses, and cancer treatment.

N-sulfonylamino acid derivatives are examples of drugs from the study that have specific inhibitory profiles against MMP-2 and MMP-9.

- **Eroglu, E.**[30]**:** This study's primary objective was to create a QSAR model in order to:Estimate the derivatives of sulfonamide-Schiff bases' inhibitory activity.

Determine which structural characteristics—such as hydrophobicity, electrical characteristics, and steric effects—have the biggest effects on CA II inhibition. Zinc-containing metalloenzyme Carbonic Anhydrase II (CA II) is essential for several physiological functions, such as breathing, pH control, and electrolyte secretion. CA II inhibitors are useful in the treatment of conditions like epilepsy, glaucoma, and some forms of cancer. Because they can interact with the zinc ion in the active site, sulphonamide Schiff bases are a class of chemical compounds that are known to inhibit CA II efficiently. a group of sulfonamide-Schiff base compounds whose CA II inhibitory actions have been experimentally evaluated and are often reported as IC_{50} or Ki values. For every chemical, a number of molecular descriptors were calculated. These comprised:

Electronic descriptors, such as the dipole moment and the HOMO-LUMO gap Parameters that are hydrophobic (like logP) Steric descriptors, like molecular volume, for example Geometrical features and topological indices.

Various models were used for the validation process like:
- Correlation coefficient (R^2)
- Cross-validation (Q^2)
- Standard error of estimate (SEE)
- F-statistics for model robustness

CA II inhibition was positively connected with the hydrophobicity of substituents on the Schiff base moiety, indicating that lipophilic groups increase action.

Activity was strongly impacted by electron-donating or withdrawing groups at particular locations, suggesting that the compounds' electrical characteristics were essential.

Steric variables also affected binding efficiency; depending on the orientation, bulky groups next to the sulfonamide moiety could either improve or hinder binding.

Activity for novel, untested compounds could be estimated with the establishment of a strong QSAR model with excellent predictive ability. A prediction method for creating novel CA II inhibitors based on sulfonamide-Schiff bases was made available by the study.

By highlighting the areas of the molecule that can be altered to increase inhibitory potency, it also provided insight into the structure–activity link. Drug discovery and optimization aimed at CA II can benefit greatly from these findings.

- **Ezabadi, I.R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Soković, M.; Glamocilija, J.; Ćirić, A[31]**: This study sought to investigate the effects of their molecular shape and lipophilicity on bioactivity by designing, synthesizing, and biologically evaluating a series of 1,2,4-thiadiazole–sulfonamide hybrid compounds for antibacterial activity. A well-known class of antimicrobials, sulfonamides frequently function as enzyme inhibitors by blocking dihydropteroate synthase and imitating para-aminobenzoic acid (PABA). An adaptable heterocyclic scaffold with well-established bioactivity, 1,2,4-thiadiazole possesses antibacterial, anti-inflammatory, and anticancer qualities. Sulfonamide and 1,2,4-thiadiazole are two pharmacophores that can be combined to create hybrid compounds with increased potency and wider spectrum action. Through multistep organic synthesis, a library of 1,2,4-thiadiazole–sulfonamide derivatives was created. Usually, under carefully monitored reaction conditions, these hybrids involved the condensation of sulfonamide moieties with substituted thiadiazoles.

The substances underwent in vitro testing against a variety of fungus, bacteria, and Gram-positive and Gram-negative organisms, including Aureus Staphylococcus, E. Coli, Candida albicans, Aspergillus niger. The antibacterial potency was assessed using the minimum inhibitory concentration (MIC).

- **Temperini et al.[32]:** This is the thorough examination of the pharmaceutical targets of carbonic anhydrases (CAs). It examines sulfonamides and their derivatives as strong carbonic anhydrase inhibitors (CAIs) and emphasizes the therapeutic value of CA isoforms.

A class of zinc metalloenzymes known as carbonic anhydrasescatalyzes the reversible hydration of CO_2 to produce bicarbonate and a proton. Numerous tissues contain it, and it plays a role in physiological functions including as control of pH, transport of CO_2, Secretion of electrolytes, Resorption of bone, 16 CA isoforms with various subcellularlocalizations are expressed by humans: The cytosolic (such as CA I and CA II),CA isoforms are targets for the following because of their extensive roles in disease: CA II and CA IV inhibitors for glaucoma, treatment of epilepsy, for overweight condition, the Zn^{2+} ion at the CA active site is directly bound by the $–SO_2NH_2$ group found in sulfonamides.

Enzymatic activity is inhibited by this interaction, which displaces a water/hydroxide ion that is coordinated to zinc.

- **Montanna et al.[33]** This study investigates the phosphodiesterase-4 (PDE4), a proven therapeutic target for inflammatory and pulmonary disorders, was the reasonable target of a novel class of sulfonamide derivatives (compounds 5, 6a–k). Known PDE4 pharmacophores served as a guidance for the structural design, which included sulfonamide moieties to improve binding affinity and metabolic stability. Docking investigations were conducted utilizing a verified PDE4 crystal structure in order to obtain insight into the molecular mechanism of inhibition. It was shown that the sulfonamide scaffold participated in important interactions with the PDE4 catalytic site, such as π–π stacking with aromatic amino acids in the binding pocket and hydrogen bonding with conserved residues. The observed structure–activity connections are supported by these interactions. Furthermore, in silico ADME profiling suggested that most compounds possess favorable oral drug-like properties, including high predicted gastrointestinal absorption, low predicted toxicity, and compliance with Lipinski's rule of five. No significant CYP450 liabilities were predicted, supporting their potential for further optimization as orally bioavailable PDE4 inhibitors.

- **Tuğrak M, Gül Hİ, Anıl B, Gülçin İ.[34]** In this study it was identified that the human isoforms of carbonic anhydrases (CAs), specifically hCA I and II, are crucial for respiration, electrolyte secretion, and pH regulation. One proven method of treating conditions including glaucoma, epilepsy, and some types of cancer is to suppress them. acetylcholinesterase (AChE) inhibition is a key mechanism in the management of neurodegenerative diseases such as Alzheimer's disease. Dual inhibition of CAs and cholinesterases presents a promising approach for addressing the multifactorial nature of neurodegeneration, combining metabolic regulation with cholinergic enhancement.

- **Wang GT, Mantei RA, Kawai M, et al.[35]: This investigation made way to** Create oral agents that are reversible and active against MetAP2. Although they had strong enzyme affinity, previous anthranilicacidsulfonamides had significant serum albumin binding, which reduced their cellular potency. The metalloenzyme Methionine Aminopeptidase-2 (MetAP2) is the target; it is necessary for the removal of N-terminal methionine from developing proteins. Being an essential modulator of angiogenesis and cellproliferation, it is a prime target for anti-cancer therapy. Impact recognition of the first micromolar hits were obtained through screening using affinity selection mass spectrometry (ASMS).With the use of co-crystal structures and MetAP2, medicinal chemists quickly refined these to nanomolar potency 5Position (R5): Heteroaryl (like 3furyl) and small alkyl (like methyl) were well tolerated. The most effective alterations for potency were O–CH_3, CH_3, and Cl at position (R6). Action Mechanism and Structural Understanding.

The binding mechanism is supported by crystal structures, such as the tetrahydronaphthalene occupying the hydrophobic pocket and the anthranilic carboxylate coordination one Mn^{2+}.

The inclusion of the tertiary amine probably alters the hydrophobic pocket contacts that albumin binds to, decreasing nonspecific sequestration. Biological Results Enzyme potency: increased to IC_{50} levels that are nanomolar.

Cellular activity: After decreasing albumin binding, improved anti-proliferative and methionine-processing effects were seen in cell-based experiments.

Drug-like behavior: Despite decreased albumin binding, tertiary amine-induced enhanced polarity decreased oral absorption, indicating a PK/PD trade-off.

- **Holmes CP, Li X, Pan Y, et al.[36]:** This study focuses on the use of novel sulfonamides as potent PTP1B inhibitors, downregulating insulin and leptin signaling is a critical function of protein tyrosine phosphatase 1B (PTP1B). Phosphate is extracted from receptor tyrosine residues. PTP1B's detrimental regulatory function on metabolic pathways makes it a well-established therapeutic target in type 2 diabetes and obesity. The inhibitors are monomeric sulfonamides with a difluoromethylene –phosphonate group that are intended to resemble phosphorylated tyrosine (pTyr), a motif that is frequently found in PTP1B inhibitors and substrates. This difluoromethylene-phosphonate functions as a mono-anionic bioisostere of a phosphate group that is non-hydrolyzable. Its binding affinity is better than that of previous carboxamide or amine analogues, improving by approximately 30 and 100 times, respectively. By substituting difluoromethylene-phosphonate, potency was significantly raised to low-nanomolar IC_{50}/K_i values, indicating strong enzyme interaction. In contrast to less complex carboxamides or tertiary amines on the same scaffold, Compared to tertiary amines, sulfonamides were around 100 times more powerful.

Compared to tertiary amines, sulfonamides were around 100 times more powerful. In comparison to earlier monoanionicgroups the difluoromethylene phosphate moiety demonstrated improved binding usefulness as a phosphate substitute, providing better contact and metabolic stability. Thephosphonate group mimics phosphate recognition by coordinating with the catalytic arginine and cysteine residues of PTP1B. By occupying nearby enzyme binding sites and forming important hydrogen bonds, the sulfonamide moiety improves affinity and selectivity.

- **Kumaran S, Gupta SP[37]:** This study centered on creating a statistical model that links the chemical structure of inhibitors that target MMP-2 and MMP-13 to their efficacy. These enzymes break down the extracellular matrix and are linked to disorders like arthritis, cardiovascular disease, and cancer metastases.

The physicochemical qualities and structural aspects of the piperidine-sulfonamide linker that connects to an aryl hydroxamic acid—the zinc-binding group (ZBG) necessary for MMP inhibition—were examined. The results showed, Clog-P, or hydrophobicity, was the main predictor of potency.Additionally important were indicator variables that highlighted particular structural motifs like:
I_1: the existence of a phenoxy piperidinyl R^1 group that has been 4 substituted.
I_1N: when a R^1 group with an NH moiety is present (only in the MMP2 model)

On analyzing the QSAR equations and insights MMP -2 model pIC50 = a+bClogP +c(ClogP)2 +dI1+eI1N

It shows an ideal hydrophobicity at ≈1.97 and a parabolic relationship with Clog P. Phenoxy R^1 increases potency when the I_1 coefficient is positive.

Negative I-N coefficient: potency is reduced by NH-containing R^1 (perhaps because the H-bond donor is not aligned with the enzyme site).

High r2 and validated vis leave-one-out cross- with q2 better than 0.6 are indicators of statistical quality.

MMP13 model
pIC50= A+BClogP+C(ClogP)2+DI1
A comparable parabolic pattern, with an ideal Clog P of ≈2.05.
shares the beneficial I_1 impact.
I_1N is not included in the MMP-13 model, indicating a distinct H-bonding environment.
After that following interpretation was obtained:
Hydrophobicity
Up to a threshold (~Cp 2.0), increasing hydrophobicity increases potency; after that, activity decreases, most likely as a result of steric mismatch in the enzyme binding pocket.
The 4-phenoxy piperidinyl R^1 group is advantageous for MMP-2 and MMP-13 structural substituents. The NH moiety in R2 is harmful to MMP-2 but not to MMP-13, suggesting that the binding site has isozyme-specific interactions.

- **Glass B., Polam P., Sparks R.B., et al.:**[38] Journal of Medicinal Chemistry, June 29, 2006, Volume 49, Issue 13, pp 3774-3789 Highlights: Developed a series of sulfonamide structures that include a difluoromethylene-phosphonate attached to a benzimidazole core. These compounds demonstrated low-nanomolar inhibitory activity against PTP1B, a key negative regulator in insulin signaling. They showed 100 times greater potency compared to tertiary amines and 30 times compared to carboxamides.A detailed discussion of the structure-activity relationship (SAR) highlighted important structural changes that improved binding.
- **M. S. Mohamed, S. M. Awad, and O. A. Fathalla:**[39] Pages 1205–1212 of Archives of Pharmacal Research, Vol. 28 (November 2005). Highlights of Pharmacology: Through Claisen-Schmidt condensations and subsequent transformations into pyrimidine, isoxazoline, pyrazoline, pyran, epoxide, and thiadiazole scaffolds, the authors created a variety of 2-thiouracil-5-sulphonamide derivatives. investigated the antifungal and antibacterial properties of these substances. Although comprehensive MIC (minimum inhibitory concentration) data is protected by a paywall, it was discovered that some derivatives exhibited noteworthy antibacterial qualities.

- The investigation was carried out by **A. Marc et al.**[40] Highlights: They coupled aminosulfonamides with adamantyl-based acyl chlorides and isocyanates to create aromatic/heterocyclic sulphonamides. They were tested for their ability to inhibit the human carbonic anhydrase isozymes CA I and CA II. The most effective compounds exhibited inhibition on par with methazolamide and acetazolamide. Experimental lipophilicity was determined (log k' IAM and ClogP), indicating the possibility of blood-brain barrier crossing. Two compounds showed >90% protection in anticonvulsant testing (MES model in mice, 30 mg/kg i.p.), with ED_{50} values of 3.5 mg/kg and 2.6 mg/kg.

- Aromatic Sulphonamides Containing Indane: **Chazellet et al.,**[41] Important Results: created aromatic sulphonamides having cores of indan-1 or indan-2 amines. Strong inhibition of hCA I (K_i = 1.6–8.5 nM) and hCA II (K_i = 2.3–12 nM) was attained. Additionally, 2 amino/acetamidoindane-5sulfonic acids were synthesized, demonstrating K_i = 43–89 nM against these isoforms. However, compared to conventional sulfonamide-based CA inhibitors, anticonvulsant activity was judged to be "rather low."

- **White & Cooper I:**[42] emphasize antimicrobial spectrum and mechanism Pharmacological Profiling of Sulfonamides (circa 2003). Broad-spectrum anti-bacterial action Sulfonamides have demonstrated broad-spectrum activity against various Gram+ bacteria and some Gram-negative bacteria, such as Klebsiella and Salmonella, Escherichia coli, Enterobacter spp., though typically resistant from Pseudomonas and Serratia. Mode of action These compounds act as competitive inhibitors of dihydropteroate synthase and thereby inhibit folic acid synthesis, the pathway essential for bacterial DNA replication. The mimicry of p-aminobenzoic acid (PABA) allows the compounds to act bacteriostatic ✳. Clinical usage and metabolism

Sulfonamides were typically used for the treatment of infections such as tonsillitis, septicemia, meningitis, dysentery, urinary tract infections, and certain fungal/protozoal diseases. The pharmacokinetics play an important role and involve the chemical properties of the sulfonamide: the pKa value related to ionization and urinary excretion (with sulfisoxazole being an example), and lipophilicity and percentage protein binding related to distribution and duration of action. Regarding side-effects and safety profile Side effects are well documented and include, crystalluria, hemolyticanemia, hypersensitivity reactions, and disruption of normal DNA methylation due to metabolism with folate

- **M. S. Y. Khan, A. Hassan, S. M. Hasan, and M. Akhter Key:[43]** pharmacological findings within the present study 2002 include= Prodrug Design: The authors synthesized a number of prodrugs of sulphonamides- these derivatives were formed to allow for an improved pharmacokinetics or to deliver the drug to a target site. Antimicrobial Activity: These compounds also displayed some measurable antimicrobial activity suggesting these compounds were likely more potent than sulphonamide drugs. Anti-Inflammatory Effects: There were some derivatives that displayed good in-vivo or in-vitro anti-inflammatory activity. Pharmacological Profiling: The authors addressed several of the essential profiling parameters e.g. antimicrobial assay (e.g MIC values), anti-inflammatory effect and preliminary observation of toxicity or side effects which aligns with the pharmacology profiling parameters typically conducted during this time in 2002.

- **R. W. Thummel, P. R. Ortiz, M. Ghosal, and M. S. Morita:[44]** Important Pharmacological Knowledge: Goal and design: A number of sulfaphenazole derivatives were created by the authors with the goal of inhibiting the cytochrome P450 2C enzymes. Profiling of enzyme inhibition: By testing these substances against the human liver's CYP2C9 and CYP2C19, it was possible to clarify structure–activity correlations and find alterations that improve the enzyme's affinity for binding. Utility of the tool-compound: These compounds functioned as chemical probes to identify minute variations in CYP2C isoforms' active site architecture in addition to inhibiting the enzyme.

- **O. Gubrynowicz, J. Cieplik, and J. Pluta:[45]** concentrated on creating novel pyrimidine-based sulphonamide compounds and assessing their antibacterial properties. Strong in vitro activity was shown by a number of derivatives, especially against Gram-positive bacteria, with some even outperforming conventional sulphonamide medications. Analysis of the structure–activity connection showed that the kind and location of substituents had a major impact on antibacterial potency. Taking into account characteristics like solubility and lipophilicity, preliminary pharmacological profiling confirmed their potential as therapeutic candidates. The study came to the conclusion that these new compounds, which combine improved biological activity, favorable physicochemical features, and synthetic accessibility, could be viable leads for future antibacterial medication development.

Remark on findings in traditional era

Between 2000 and 2014, sulphonamides shifted from traditional antibacterial agents to multi-functional drug candidates with a wide scope of therapeutic applications. Due to their relative structural simplicity, chemical flexibility, and broad biological target range, sulphonamides became interesting scaffolds available to drug designers today.

The research undertaken from approximately 2000 and 2014 has opened the door to many avenues other than antibacterial research for sulphonamides in fields such as cancer therapy, enzyme inhibition, diabetes, anti-inflammation and other therapeutic avenues. In particular, sulphonamides became significant via modulation of carbonic anhydrase and other clinically important enzymes.

The combination of computational modeling, synthetic chemistry, and pharmacological screening propelled the research into selective/active sulphonamide derivatives with improved pharmacokinetic and safety properties. At the same time, the renewed interest in sulphonamide acceptance coincides with increased complexity in therapeutic target identification across the biology with increasing rates of drug resistance.

To conclude, sulphonamides are an interesting, versatile, and promising class of compounds. Continued research and optimal development may open up more paths to address require medical needs and shortcomings for next generation therapeutics.

CONCLUSION

A comparison between the periods 2025-2015 and 2014-2000 indicates a transition in mindset and progression in sulphonamides. Between 2000 and 2014, sulphonamides were researched mainly based on the use of existing drugs and little new development took place, which was mainly focused on how to counteract microbial resistance and the optimization of existing drugs. Even during this period there were few novel derivatives and even fewer were used in clinical practice due to the awareness of considerable adverse effects caused by severe hypersensitivity reactions. The difference between the periods from 2015 to 2025 is a revival in sulphonamide studies with a dominantly focus on developing novel derivatives, using advanced drug design technologies. Newer sulphonamides, whether natural or synthetic, appear more effective than previously used formulations and encouraged repurposing as anticancer and anti-inflammatory therapeutic agents, that take advantage of the safety profile and included targeted delivery systems. The later decade seems more stewardship consistent with innovative and patient-centered, to develop more effective, safer, and versatile products; conversely, the earlier decade can be described as lacking innovation, with less safe potentially limited practice.

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