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Review on Sulfonamides

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ABSTRACT

Using structural and molecular data from a chemical library, quantitative structure-activity relationship (QSAR) modeling involves creating prediction models of biological activities. The term "quantitative structure-property relationship" (QSPR) refers to the concept of QSAR, which is typically used for drug discovery and development and has found widespread application for correlating molecular information with not only biological activities but also with other physicochemical properties. Finding correlations between chemical structures and biological activity is done using the widely utilized predictive and diagnostic method known as QSAR. In an effort to meet the requirement and desire of medicinal chemists to anticipate biological response, QSAR has developed throughout time. Recent work has reported anticancer, antibacterial, carbonic anhydrase inhibition activity, radiosensitizers, SARS-CoV-2 inhibitors, aromatase inhibitors, antidiabetic agents, BRAFV600E Inhibitors, antioxidative and antimalarial studies. This review covers the concept, and also the components involved in the synthesis and development of QSAR models.

INTRODUCTION

The first antimicrobial medications to be effectively produced are sulfonamides. The antibacterial activity is mediated by a competitive suppression of folic acid synthesis, which stops microbial growth and reproduction. Sulfonamides are categorized as bacteriostatic agents because of their mode of action. Sulfonamides are still the preferred medications for the treatment of a number of ailments and disorders even though they have been used in therapy for more than 70 years. Bacterial resistance and sulfonamide adverse effects restrict the use of sulfonamides in treatment.

Numerous sulfonamide derivatives were formed during the beginning phases of the study of sulfonamides, prompting researchers to establish a link between certain structural traits and the antibacterial activity of recently developed compounds. First and foremost, the action of sulfonamides depends on the presence of a free aromatic NH_2 group in the para position with respect to the sulfonamide group. The sulfonamide activity is decreased by the extra substituent in the ortho and meta positions of the benzene ring. Sulfanilamide's N_1-monosubstituted derivatives are active substances whose degree of activity rises with the addition of heteroaromatic substituents. Compounds that have two substitutions in the N1 position are inert. In addition, the benzene ring and the sulfonamide group must be joined directly. The diminution or total loss of activity also results from replacing the benzene ring with another cyclic system. Gram-positive and certain Gram-negative bacteria, including intestinal bacteria *Escherichia coli, Klebsiella, Salmonella, Shigella*, and *Enterobacter* species, are both susceptible to the antimicrobial effects of sulfonamides, which have a broad range of activity. Sulfonamides have strong antimicrobial action against *Klebsiella*, excellent antimicrobial activity against *E. coli*, moderate antimicrobial activity against *Proteus mirabilis* and *Enterobacter* species, and no antimicrobial activity against *Serratia* and *Pseudomonas aeruginosa*. They are efficient against the *Chlamydia* genus species. Sulfonamides are also efficient against *Toxoplasma gondii, Pneumocystis carinii*, and protozoa. The antibacterial activity spectrum of sulfonamides does not alter depending on their potency.

The objectives and biological activity of sulfonamide molecules are quite diverse. The chemistry of sulfonamide plays a part in both its production in various forms and its blending with other substances to boost its potency against certain ailments. The use of sulfonamide derivatives as an anti-cancer agent is now being studied, in addition to their historical usage

as anti-inflammatory agents and their application to the treatment of Alzheimer's disease. the use of sulfonamide compounds in treating multiple diseases, including anticancer, antimicrobial, etc. There are numerous derivatives associated with sulfonamide and modern strategies to manufacture it in different forms. (1, 2)

LITERATURE REVIEW

Ratchanok Pingaew et al. (2015) reported Novel 1,4-naphthoquinone-based sulfonamides. The investigated cancer cell lines included HuCCA-1, HepG2, A549, and MOLT-3, and all quinone-sulfonamide derivatives showed a wide range of cytotoxic effects against each of them. The majority of quinones (33-36 and 38-43) had more anticancer activity against HepG2 cells than etoposide did. The most powerful compounds were found to be the open-chain analogs 36 and 42. Notably, the 6,7-dimethoxy group-containing limited sulfonamide analog 38 had the strongest antimalarial activity (IC_{50} = 2.8 μM). To identify key chemical characteristics controlling the biological activities, a quantitative structure-activity relationships (QSAR) investigation was carried out. The prediction performance of five built QSAR models (Rcv 0.5647-0.9317 and RMSEcv 0.1231-0.2825) was satisfactory. The activities of four more sets of structurally altered compounds (34a-34d, 36a-36k, 40a-40d, and 42a-42k) were predicted using the established QSAR models. (3)

Azhar Salari-Jazi et al. (2021) investigated Synthesis, 3D-QSAR studies, and antibacterial evaluation of some novel coumarin isoxazol sulfonamide hybrid compounds. In five phases, beginning with coumarin-3-carboxylic acid and 3-amino-5-methyl isoxazole, many new sulfonamide hybrids, containing the coumarin and isoxazole group, were created and tested for their antibacterial properties. The samples were produced with a good to high yield, and they were examined using FT-IR, ^{13}C-NMR, ^{1}H-NMR, and melting point methods. By using the agar diffusion technique, the antibacterial activity of the synthesized sulfonamide base hybrids (9a-l) was examined against E. coli and S. aureus. The total expense of an experimental drug test is significantly reduced by the use of the quick, simple, cost-effective, and high throughput screening approach known as 3D-QSAR to anticipate the influence of a compound's efficacy. Finding r^2 and q^2 the pMIC of the intended molecule using the 3D-QSAR model demonstrated adequate predictive and descriptive capacity. Using this approach, it is possible to explain key characteristics that depend heavily on antibacterial activity. In accordance with this hypothesis, based on the pMIC, the sulfonamide hybrids 9b and 9f had the greatest impact on gram-negative and gram-positive bacteria. The actual tests

validated the 3D-QSAR results, indicating the value of our approach for creating novel antibacterial compounds. (4)

Zhifen Lin et al. (2019) reported a QSAR-based investigation on antibiotics facilitating the emergence and dissemination of antibiotic resistance genes as a case study of sulfonamides against mutation and conjugative transfer in Escherichia coli. The developed QSAR models show that sulfonamides (SAs) may boost the FtsZ protein and pili production in E. coli by binding to the SdiA protein, eventually resulting in SAs facilitating growth, mutation frequency, and conjugative transfer frequency. According to the findings, SAs can exert selection pressure on E. coli to encourage the establishment and spread of Antibiotic resistance genes (ARGs). This work offers a fresh angle for the mechanistic evaluation of ARG pollution as well as reference data for subsequent research on the development and spread of ARGs under antibiotic exposure. (5)

Kathiravan M. K. et al (2021) evaluated Docking studies and molecular dynamics simulation of triazole benzene sulfonamide derivatives with human carbonic anhydrase IX inhibition activity. The hypoxia endogenous marker carbonic anhydrase IX has been employed in a variety of solid malignancies, including cancers of the head and neck, lung, bladder, and renal cells. -CA IX isozyme is overexpressed in hypoxic environments, making it a desirable target for the development of inhibitors that specifically target cancer and tumor invasion and progression. The bioactivity of new leads was predicted using the statistically confirmed QSAR model. Additionally, research on molecular docking and molecular dynamic modeling were conducted on the proposed compounds with high scores. Using QSAR model 2, the bioactivity of the designed compounds 1, 2, 20, 24, and 27 was expected to be 9.13, 9.65, 10.05, 10.03, and 10.104 logarithmic units, respectively. The following compounds' low energy conformations interacted with Gln92, Thr200, Asn66, and His68 and had good Autodock binding energy scores (8.1, 8.2, 8.1, 8.3, and 9.2 K cal mol^{-1}). Desmond's research of human carbonic anhydrase IX inhibition using molecular dynamics simulations for 100 ns of compound 27 in comparison to reference SLC0111 yielded insightful structural information. Hydrophobic and hydrophilic stable interactions were identified in compound 27's novel chemical structure at the active site. Analysis using RMSD, RMSF, RoG, H-bond, and SASA demonstrated that compound 27 binds to the 5FL4 structure in a stable manner. Additionally, the docking findings are also supported by MM-PBSA and MM-GBSA. As the best theoretical lead that can be further investigated experimentally for selective inhibition, we suggest the developed compound 27 (predicted Ki ~ 0.07 nM). (6)

Kunal Roy et al. (2021) evaluated QSAR and QSAAR modeling of nitroimidazole sulfonamide radiosensitizers. To create 2D quantitative structure-activity relationship (QSAR) models and identify the structural characteristics required for the radiosensitizer enhancement ratio and survival ratio, researchers used 21 nitroimidazole sulfonamide analogues. Small dataset modeler software was used to create the models, and a number of rigorous validation criteria were used to do model validation. The created models are reliable, predictive, and ought to be effective instruments for predicting the radio sensitization of nitroimidazole sulfonamides. 14 external nitroimidazole sulfonamide compounds to test the predictive power of the created models using the "prediction reliability indicator" tool. Quantitative structure-activity relationship (QSAAR) models have also been created for the two endpoints. (7)

Devaanshi Jagwani (2023) investigated QSAR and Quantum chemical study of sulfonamide derivatives with Carbonic Anhydrase (CA-II) Inhibitory Activity and its probabilistic Molecular Dynamic simulation approach. The present research studied QSAR on numerous bioactive sulfonamide compounds and used the molecular mechanics (MM) technique and the MM+ force fields to perform initial geometry optimizations for all of the compounds. The lowest energy conformations of the compounds produced by the MM approach were improved using the density functional theory (DFT) method employing Becke's three-parameter hybrid functional (B3LYP) and the 6-31G (d) basis set. The estimation of the compounds' ability to inhibit carbonic anhydrase (CA-II) is greatly aided by the following parameters derived from DFT calculations: molecular descriptors, dipole moment, electro negativity, total energy at 0 K, entropy at 298 K, HOMO and LUMO energies. These parameters also provide significant information. To determine the compounds' descriptors and carbonic anhydrase (CA-II) inhibitory data, several QSAR models were developed using the multiple linear regression approach. The five-parameter linear equation that makes up the statistically most important of the aforementioned QSAR models has squared correlation coefficient R^2 values of around 0.7629 and adjusted correlation coefficient R^2_A values of about 0.6612. In the context of regulatory factors, the inhibitory action of carbonic anhydrase (CA-II) was examined. The use of Molecular Dynamic Simulation tools to examine the therapeutic potential of pharmaceuticals and antibodies is expected to have a promising future for computer-aided drug development. (8)

Jian-Bo TONG et al. (2021) evaluated Molecular design, molecular docking, and ADMET study of cyclic sulfonamide derivatives as SARS-CoV-2 inhibitors. Using three-dimensional

quantitative structure-activity relationships (3D-QSAR) and holographic quantitative structure-activity relationships (HQSAR), the structural and activity interactions of 35 cyclic sulfonamide compound inhibitors are studied. The Topomer CoMFA model (q^2 = 0.623, r^2 = 0.938, r^2_{pred} = 0.893) and the HQSAR model (q^2 = 0.704, r^2 = 0.958, r^2_{pred} = 0.779) are two models with high statistical parameters and trustworthy prediction performance. The established models exhibit strong external prediction capability for the test set in addition to high stability. This information leads the way for the creation of four novel cyclic sulfonamide compounds and predicts their pIC_{50} values. The contour and color code maps of the models offer a wealth of relevant information for understanding the structural requirements that could impact the activity. The docking results suggest that the SARS-CoV-2 inhibitor under consideration in this work may contain the possible active residues GLU166, GLN192, ALA194, and VAL186. The results indicate that the four newly developed cyclic sulfonamide compounds exhibit significant ADMET qualities and may be employed as trustworthy inhibitors against COVID-19. Next, the oral bioavailability and toxicity of the newly designed cyclic sulfonamide compounds are examined. These findings could be insightful in developing potent SARS-CoV-2 inhibitors. (9)

Y. Entezari Heravi et al. (2017) reported 3D QSAR studies, pharmacophore modeling, and virtual screening of diaryl pyrazole–benzene sulfonamide derivatives as a template to obtain new inhibitors, using human carbonic anhydrase II as a model protein. The findings show that the q^2 values for CoMFA and CoMFA-RF were comparable to 0.703 and 0.742 with three components, respectively. This indicates the dependability and robustness of these models. The CoMFA-RF is superior to the common CoMFA, according to statistical comparisons of the findings. the actual pKi against predicted pKi values for the compounds in the training, test, and evaluation sets based on CoMFA, CoMFA-RF, and COMSIA models. Other statistical parameters were as follows: r^2_{ncv}=0.856 and 0.862, r^2_{pred}=0.891 and 0.742, F_{value} (Fischer ratio) of 43.584 and 45.959, SEE (low standard error of estimation) of 0.312 and 0.305 with a column filtering of 0.3 kcal/mol for both CoMFA and CoMFA-RF, respectively. The findings show that the q^2 values for CoMFA and CoMFA-RF were comparable to 0.703 and 0.742 with three components, respectively. This indicates the dependability and robustness of these models. The CoMFA-RF is superior to the common CoMFA, according to statistical comparisons of the findings. Due to the expansion of NH_2 substitution in the right direction from the -$CONH_2$ group, compounds 36 and 37 that contain hydrazine groups exhibit strong inhibitory efficacy. Additionally, it shows that the aligned molecules are

inactive compared to acetazolamide (AZA). Comparing the most and least active chemicals found in AZA revealed that their activity was reduced when the necessary replacement for these compounds wasn't present in the appropriate area of the green contours. Therefore, these compounds' poor activity can be linked to their electrostatic properties. As seen, red contours surrounding the substituent on the pyrazole and sulfonamide rings illustrate increasing the activity of compounds by adding electron acceptor groups to this region. Furthermore, the addition of 4-fluoro-phenyl to compound 26 greatly boosted this molecule's activity. This proves that there exist amino acids with electron donor properties in the active site of hCAII, allowing them to interact with their auxiliary functional groups of a molecule with an electron acceptor characteristic. Sulfonamide groups may properly connect with the amino acids His119 and Thr199 since they are electron acceptors. The blue spots around the 5-sided pyrazole ring showed how the activity of the molecule may be boosted by adding considerably more constrained electron donor groups there. (10)

Hamilton B. Napolitano et al. (2021) evaluated sulfonamide chalcone with potential antineoplastic application. A sulfonamide chalcone with potential antineoplastic use, 1-Benzenesulfonyl-3-(4-bromo benzylidene)-2-(2-chlorophenyl)-2,3-dihydro-1H-quinolin-4-one, was synthesized. It also underwent a thorough structural analysis. The sulfonamide chalcone also fits well in the ligand-binding site of the EGFR, according to in silico tests, with seven-alkyl binding energy interactions on the ligand-binding site. Finally, the spatial features required for the possible action of sulfonamide chalcone as an antagonist were shown by the kinetic stability and pharmacophoric analysis for EGFR. (11)

Zhemin Shen et al. (2022) reported A QSAR study investigation of influencing factors on the degradation of sulfonamide antibiotics in iron-impregnated biochar-activated urea-hydrogen peroxide system. A three-dimensional quantitative structure-activity relationship (3D-QSAR) model based on molecular force field and a two-dimensional quantitative structure-activity relationship (2D-QSAR) model based on quantum chemical parameters were developed to study the factors influencing the removal efficiencies (Re%) in order to better understand the degradation of sulfonamide antibiotics by FB-activated UHP. With evaluation indices of 0.732, 0.571, and 0.673, the ideal 2D-QSAR model has Re%= 0.858-8.930 E-5 -0.175. The provided 2D-QSAR model suggested that the intrinsic elements affecting Re% were the molecule size and the Fukui index with regard to nucleophilic attack. Following the distribution, three degradation mechanisms were suggested. With assessment indices of R^2 = 0.989, q^2 = 0.696, and SEE= 0.001, the constructed 3D-QSAR model

demonstrated greater prediction ability than the 2D-QSAR model. According to the examination of field contribution rates, the key variables affecting Re% were electrostatic field (48.2%), hydrophobic field (25.3%), and hydrogen-bond acceptor field (12.7%). These results produced vital data for assessing the mechanisms and rules governing degradation and offered theoretical support for the initial estimation of the Re% of sulfonamide antibiotics through the FB-activated UHP process. (12)

Ratchanok Pingaew et al. (2019) reported Synthesis, molecular docking, and QSAR study of bis-sulfonamide derivatives as potential aromatase inhibitors. Except for compound 23, all bis-sulfonamide derivatives inhibited the aromatase with an IC_{50} range of 0.05-11.6 μM. With sub-micromolar IC_{50} values (i.e., 50 and 60 nM, respectively), the hydrophobic chloro and bromo groups in the analogs 15 and 16 showed strong aromatase inhibitory action with a good safety index. By mimicking the steroidal backbone of the natural substrate, androstenedione, the chloro and bromo benzene sulfonamides (15 and 16) may bind hydrophobically with Leu477 of the aromatase. This was discovered using molecular docking. The results of the QSAR analysis also showed that the van der Waals volume (GATS6v) and mass (Mor03m) descriptors were responsible for the most effective action of the compounds. The two compounds (15 and 16) were finally singled out as potentially useful molecules for further research into new aromatase inhibitors. (13)

Ratchanok Pingaew et al. (2018) investigated the Synthesis, molecular docking, and QSAR study of sulfonamide-based indoles as aromatase inhibitors. The IC_{50} range for all indole compounds was 0.7-15.3 μM, inhibiting the aromatase. Indoles (27–36) had more aromatase inhibitory action than did ketoconazole. The most powerful compounds with sub-micromolar IC_{50} values (i.e., 0.7 and 0.8 μM, respectively) without damaging the normal cell line were found to be the phenoxy analogs 28 and 34 with the methoxy group. Molecular docking showed that the indoles 28, 30, and 34 could occupy the same binding site on the aromatase pocket and share multiple binding residues with those of the natural substrate (androstenedione), which suggested that competitive binding might be the way of inhibiting the compounds. The strongest analog 28, when combined with the MET374 and ASP309 residues on the aromatase, might imitate the H-bond interactions of genuine androstenedione. The para-phenoxy indole (28) has a larger value of the electronegativity descriptor MATS6e and has stronger inhibitory action when compared to the ortho-phenoxy compound (34), according to the QSAR model. A number of intriguing indoles that might be made into new aromatase inhibitors for medicinal purposes were identified in the study. (14)

Balasubramanian Narasimhan et al. (2014) evaluated Synthesis, antimicrobial, anticancer, antiviral evaluation, and QSAR studies of 4-(1-aryl-2-oxo-1,2-dihydro-indol-3-ylidene amino)-*N*-substituted benzene sulfonamides. The in vitro antibacterial, antiviral, and cytotoxic properties of a series of 4-(1-aryl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-N-substituted benzenesulfonamide derivatives (1-32) were studied. Compounds (11) and (18) were shown to be the most efficient antimicrobial compounds, according to the data. The synthetic chemicals acted fungistatically and bacteriostatically in general. The compounds were shown to be less active than the common medicine 5-fluorouracil (5-FU), according to the findings of the cytotoxic screening. At subtoxic levels, none of the substances prevented virus replication. In general, the inclusion of an ortho- and para-substituted benzoyl moiety and a pyrimidine ring with electron-releasing groups promoted antibacterial activity. The findings of QSAR investigations showed how crucial topological characteristics, including valence zero order molecular connection index ($^{0}\chi^{v}$) and valence first order molecular connectivity index ($^{1}\chi^{v}$), are in defining the antibacterial activity of produced drugs. (15)

Lakshman R. Meena et al. (2020) investigated the Synthesis, QSAR, and DFT analysis of sulfonamide chalcones as potential: antimicrobial, antifungal, and antimalarial agents. Different aromatic aldehydes combine with aryl ketone (N-(4-(phenyl sulfonamido) phenyl) acetamide) in the presence of aqueous alkaline NaOH to create, -unsaturated ketone (N-(4-(N-phenyl sulfamoyl)phenyl)cinnamamide derivatives or sulfonamide chalcone derivatives). Through the Claisen-Schmidt condensation of aromatic aldehydes and sulfonamide containing acetanilide, we were able to create new sulfonamide chalcones. Mass, FTIR, and NMR (^{1}H & ^{13}C) spectra analyses were used to describe all the produced compounds. The antibacterial activity of the target sulfonamide chalcone compounds (2a–2m) was compared with standard drugs of “Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin” in the Agar well diffusion method. E. coli, P. aeruginosa, S. aureus, and S. pyogenus are examples of bacterial strains. Compounds 2a, 2k, and 2m also have stronger potential against S. pyogenus than do compounds 2e, 2l, and 2j against P. aeruginosa, E. coli, and S. aureus, respectively. All six of the aforementioned compounds—2e, 2l, 2j, 2a, 2k, and 2m—have higher potential and have MIC values of 50 mg/ml or above. While seven compounds, with MIC values of 62.5 mg/ml, 2b, 2d, 2f, 2k, 2m, 2c, and 2g, were shown to have intermediate antibacterial activity. The increased antibacterial activity (MIC value is 50 mg/ml) was demonstrated by the sulfonamide chalcones with the 2a, 2l, 2j, 2m (methoxy group), 2e (pyridine moiety), and 2k (-OH group). Sulfonamide chalcones with the 2b, 2d (fluoro

group), 2f (both -OCH_3 and -OH group), 2k, and 2c (hydroxyl group), as well as the 2m and 2g (-OCH_3 group), were shown to be intermediate in activity. All of the recently created sulfonamide chalcone compounds were examined for in vitro antifungal activity utilizing the agar diffusion technique and three different fungi, including C. albicans, A. niger, and A. clavatus. The majority of the compounds showed substantial antifungal potential. Most chemicals were shown to have stronger potential against C. albicans, according to evaluation. While compounds 2b, 2c, 2d, 2e, 2f, 2h, 2i, 2k, and 2m display intermediate antifungal activity with MIC values of 500 mg/ml, compounds 2a, 2g, 2j, and 2l are discovered to have better potential against C. albicans. Additionally, it was shown that most substances had decreased antifungal effectiveness against A. clavatus. The sulfonamide chalcones with the methoxy group (2a, 2g, 2j & 2l) showed the greatest antifungal activity (MIC value 250 mg/ml). About thirteen sulfonamide chalcones were tested for antimalarial activity, and it turns out that, four drugs, with Mean IC_{50} (P. falciparum, µg/ml) values of 0.83, 0.37, 0.54, and 0.61 respectively, shown higher antimalarial activity. Different compounds with Mean IC_{50} (P. falciparum, g/ml) values larger than one had weaker antimalarial activity. Quinine and Chloroquine were utilized as reference medicines. Alkoxy-containing compounds (2a, 2e, and 2j) with aromatic rings have great biological efficacy. Additionally, we have discovered that the aromatic ring's antimalarial activity is increased by the presence of a hydroxyl substitution group (2k). All of these findings open up a wide range of new opportunities and promise to enhance the antimalarial activity of sulfonamide chalcone derivatives. (16)

Qin-Lu Lin et al. (2022) reported Precise Hapten Design of Sulfonamides by Combining Machine Learning and 3D-QSAR Approaches. The chemical structure of the hapten utilized to produce the immunogen largely determines the cross-reactivity (CR) of monoclonal antibodies (mAb). Hapten structures are frequently created using experience and then experimentally validated. In the present study, the association between the sulfonamides (SAs) structures and the CR of the previously produced broad-specific mAb 2G3 was examined in order to build accurate machine-learning models and a reliable comparative molecular field assay (CoMFA). Based on the knowledge gained from the model study of mAb 2G3, a novel hapten that corresponds to mAb 3D1 and has superior qualities was created. Additionally, the additional mAb 3D1 models were created and assessed. Finally, by comparing the benefits and drawbacks of the two models of the antibodies 2G3 and 3D1, a supplementary analytical technique was developed to elucidate the structural variables and

physicochemical aspects that influenced the CR of the mAb. The suggested method can serve as a useful guide for future exact hapten structure alteration in other projects of a like nature. (17)

Jarosław Sławińsk et al. (2015) investigated the Synthesis, Molecular Structure, Metabolic Stability, and QSAR Studies of a Novel Series of Anticancer N-Acyl benzene sulfonamides. Novel N-acyl-4-chloro-5-methyl-2-(R1 -methyl thio) benzene sulfonamides 18–47 have been made by reacting N- [4-chloro-5-methyl-2-(R1 -methyl thio) benzene sulfonyl] cyanamide potassium salts with the proper carboxylic acids. With growth percentages (GPs) ranging from 7% to 46%, several of them showed anticancer efficacy toward the human cancer cell lines MCF-7, HCT-116, and HeLa. Using the topological, ring, and charge descriptors based on the stepwise multiple linear regression approach (MLR), quantitative structure-activity relationship (QSAR) investigations were conducted on the cytotoxic activity of N-acyl sulfonamides against MCF-7, HCT-116, and HeLa. Three predictive and statistically significant models for the examined chemicals were discovered by QSAR investigations. The outcomes of these models showed that topological distances, the number of ring systems, the maximum positive charge, and the number of atom-centered fragments all affect the anticancer activity of N-acyl sulfonamides. On a pool of human liver microsomes and NADPH, the metabolic stability of the chosen compounds had been assessed; both the R1 and R2 substituents of the N-acyl sulfonamides concurrently impacted them. (18)

Agrawal VK et al. (2023) investigated QSAR Studies on Some Sulfonamides as Antidiabetic Agents using topological descriptors. Using descriptors generated by the Dragon program, the activity in terms of pKi has been modeled. After two outliers were removed, the best model with an R^2 value of 0.9897 was provided. Cross-validation was used to test the model. The stated five-parametric model's R^2_{cv} value comes out to be 0.9896. Additionally, collinearity and defect of chance have been examined in the model. The model's defect-free status has been confirmed. (19)

Pradeep Kumar et al. (2022) evaluated Gaussian field-based 3D-QSAR and molecular simulation studies to design potent pyrimidine–sulfonamide hybrids as selective BRAFV600E Inhibitors. In melanoma, the "RAS-RAF-MEK-ERK" pathway is a crucial signaling mechanism. In this pathway, BRAFV600E (70–90%) is the most frequent mutation. Type I (aC-IN/DFG-IN), type II (aC-IN/DFG-OUT), type I1/2 (aC-OUT/DFG-IN), and type I/II (aC-OUT/DFG-OUT) conformers are the four different types of BRAF inhibitors. First-

and second-generation BRAF inhibitors are ineffective against cancers brought on by dimer BRAF mutations that cause "paradoxical" activation and are resistant to BRAFV600E. In the current work, we used 3D-QSAR, molecular docking, and molecular dynamics simulations to carry out molecular modeling of inhibitors of pyrimidine-sulfonamide hybrids. Using 3D-QSAR analysis, new pyrimidine sulfonamide hybrid BRAFV600E inhibitors were discovered. The proposed compounds are structurally related to a number of first- and second-generation BRAF inhibitors' structural moieties. Molecular docking investigations were carried out using a library of 88 designed compounds in total. Hits were found for four molecules (T109, T183, T160, and T126), which were then chosen for in-depth analysis. The binding was estimated after 900 ns of molecular dynamics simulations. The proposed compounds exhibit improved interactions with the core active site [the nucleotide (ADP or ATP) binding site], according to molecular docking and simulation studies. DFG motif, and the BRAFV600E protein's phospho-acceptor site (activation region) than earlier inhibitors. The developed compounds contain [aC-OUT/DFG-IN] structure, just as the FDA-approved BRAFV600E inhibitors. T126, T160, and T183 compounds interacted with DIF (Leu505) and may be effective against BRAFV600E resistance and cancers brought on by dimer BRAF mutations. The proposed compounds are now being synthesized and biologically evaluated, which might produce some effective BRAFV600E selective inhibitors. (20)

Apilak Worachartcheewan et al. (2022) reported the synthesis of antioxidative and QSAR studies of acetamido sulfonamide derivatives. The antioxidant (radical scavenging and superoxide dismutase (SOD)) and antibacterial properties of a series of sixteen acetamido sulfonamide derivatives (1–16) have been studied. The majority of compounds demonstrated antioxidant properties, with compound 15 showing the strongest SOD and radical scavenging properties. Using multiple linear regression, the quantitative structure-activity relationship (QSAR) has been explored. The created QSAR models have good correlation coefficients (for RSA and SOD activities, respectively, $Q^2_{LOO\text{-}CV}$ = 0.9708 and 0.8753) but low root mean square errors ($RMSE_{LOO\text{-}CV}$ = 0.5105 and 1.3571, respectively). A connection between an ethylene group and a pyridine ring offered considerable antioxidant capabilities, according to the structure-activity relationship. (21)

Erol Eroglu (2008) investigated QSAR Studies for a Group of Sulfonamide Schiff bases as Carbonic Anhydrase CA II Inhibitors using Codessa Pro methodology and software. A linear regression Using Codessa Pro software, QSAR models of the biological activity (Ki) of 38

inhibitors of the carbonic anhydrase CA-II isozyme were developed. These models used 12 different molecular descriptors that were chosen from among more than a thousand geometrical, topological, quantum-mechanical, and electronic types of descriptors. The statistically most significant model among those provided in this study is a five-parameter equation with a correlation coefficient, R^2 value of around 0.840, and a cross-validated correlation coefficient, R^2 value of about 0.777. An ethylene group linked to a pyridine ring demonstrated a substantial antioxidant activity relationship. (22)

David E. Reichert et al. (2009) reported Docking and 3D-QSAR Studies on Isatin Sulfonamide Analogues as Caspase-3 Inhibitors. A series of 59 isatin sulfonamide analogs were docked to the X-ray structure of caspase-3, one of the key cysteine aspartyl-specific execution proteases in apoptosis, in order to shed light on their inhibition mechanism and make it easier to design more effective ligands. Studies using comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) reveal that hydrophobic interactions account for the majority of the steric and electrostatic contributions to the compounds' binding affinity. Even under the strictest evaluation standards for a QSAR model, the models exhibit great correlation and strong predictive power. The findings of this study show that structure-based design techniques, such as docking, encourage the creation of trustworthy QSAR models and highlight the value of this strategy in the production of fresh, powerful caspase-3 ligands. (23)

T. Ahmad et al. (2020) investigated In vivo Anti-Diabetic Studies of Sulfonyl urea Sulfonamide Hybrids. By reacting the simple 4-aminobenzenesulfonamide molecule with aryl sulfonyl chlorides, it was possible to create sulfonamides and sulfonylurea-sulfonamide hybrids. By performing an oral glucose tolerance test (OGTT) percentage analysis on Sprague Dawley (SD) rats at a dosage of 20 mg/kg while using glibenclamide (GC), the anti-diabetic properties of these pharmacophores were examined. Six of these synthesized pharmacophores showed a percentage reduction in blood glucose level at 20 mg/kg dose compared to glibenclamide (74 3.10% reduction) at 50 mg/kg dose of glibenclamide after 2 and 5 hours of oral administration, respectively (20.47 ±2.54 to 44.97 ±2.16%) and (20.79 ±1.55 to 37 ± 2.94%). Recent research suggested that these chemicals may make a great complement to medications used to reduce elevated blood glucose levels in people with diabetes mellitus. (24)

MF Zhang et al. (2022) evaluated the synthesis and pharmacological characterization of N-(3-ethylbenzo[d]isoxazol-5-yl) sulfonamide derivatives as BRD4 inhibitors against acute myeloid leukemia. BRD4 has been identified as a promising target for the treatment of cancer because it plays a significant role in the control of gene transcription. 26 novel compounds were prepared by adding sulfonamides to the core of 3-ethyl-benzo[d]isoxazole. The majority of the compounds had strong BRD4 binding capabilities with Tm values greater than 6 °C. To analyze the binding patterns, two crystal structures of 11h and 11r in complex with BRD4(1) were obtained. With IC_{50} values of 0.78 and 0.87 μM, compounds 11h and 11r demonstrated impressive anti-proliferative activity against MV4-11 cells and were successful in binding to BRD4(1). Additionally, in MV4-11 cells, 11r (0.5–10 μM) suppressed the expression of oncogenes including c-Myc and CDK6 in a concentration-dependent manner. (25)

Mogedda E. Haiba et al. (2021) reported Synthesis, antimicrobial evaluation, and QSAR study of potent antimicrobial agents of new tetrahydronaphthalene-sulfonamide derivatives, derived from new easily synthetic route of 3-methoxy-8-oxo-5,6,7,8-tetrahydronaphthalene-2-sulfonyl chloride 2. The in vitro antibacterial inhibitory properties of each produced compound were evaluated against a range of Gram-positive and Gram-negative bacterial pathogenic strains as well as Candida albicans. Compound 2 had low action against all of the pathogenic strains that were examined, although it is readily changed into biologically active sulfonamide products 5a–f or moderately active compounds 3a–k from its original state of biological inactivity. The potential candidates 5d and 5e's cytotoxic assessment revealed a notable safety profile against human normal cells. A QSAR research for the novel compounds was conducted, and the results correlated with the antibacterial ones. (26)

M. K. Kathiravan et al. (2022) evaluated molecular field-based QSAR studies and docking analysis of mercaptoquinazolinone benzene sulfonamide derivatives against hCA XII. The tumor-associated hCA XII isozyme can be selectively targeted in order to provide more potent and secure cancer therapies. To create 3D-QSAR models, a series of mercapto-quinazolinone benzene sulfonamide derivatives were submitted to molecular field analysis. Utilizing the Molecular Design Suite of V-life MDS 4.6 Software, structural characteristics including physicochemical, topological, electro-topological, and quantum-chemical descriptors were determined. The contour map produced by the SA-kNN model demonstrates the importance of electrostatic and steric characteristics for the interaction between hCA XII

and its binding. Studies on molecular docking favored structural discoveries in conjunction with QSAR. Asn67, Gln92, Thr199, and His119 were the most interdependent residues, stabilizing the chemicals in the active pocket. The results obtained highlight crucial binding characteristics of mercaptoquinazolinone benzene sulfonamide derivatives against hCA XII and propose structural insights that can be used to design and create powerful leads. (27)

Baoan Song et al. (2022) evaluated Novel Cytosine Derivatives Containing a Sulfonamide Moiety as Potential Antiviral Agents. The antiviral properties of many cytosine derivatives with sulfonamide moiety were developed, synthesized, and comprehensively tested against the pepper mild mottle virus (PMMoV). The structure-activity connection was then investigated using a three-dimensional quantitative structure-activity relationship (3D-QSAR) model based on the pEC_{50} of the compound's protective effects. The CoMSIA and CoMFA models were then used to create compound A32, which had preferred antiviral activity against PMMoV and had an EC50 of 19.5 μg/mL, outperforming the template molecule A25 (21.3 μg/mL) and ningnanmycin (214.0 μg/mL). Further investigations revealed that the up-regulation of proteins involved in the defensive response and carbon fixation in photosynthetic organisms was consistent with the antiviral activity of compound A32 against PMMoV. These findings suggested that fresh potential antiviral medicines for more study and development may be derived from cytosine derivatives with a sulfonamide component. (28)

Samar H. Fahim et al. (2022) reported the Design and synthesis of ciprofloxacin-sulfonamide hybrids to manipulate ciprofloxacin pharmacological qualities. It was discovered that changes at the N atom of the side chain's C_7 helped to increase absorption, activity, and side effects. Nineteen novel ciprofloxacin-sulfonamide hybrid compounds were developed, synthesized, and characterized by IR, ^{1}H NMR, and ^{13}C NMR as prospective antibacterial agents with dual DNA gyrase/topoisomerase IV inhibitory action to fulfill the growing need for new antibacterial drugs. By evaluating their inhibitory action against DNA gyrase, DNA topoisomerase IV, as well as their minimal inhibitory concentration against Staphylococcus aureus, the majority of the synthesized compounds demonstrated strong antibacterial activity. In comparison to ciprofloxacin (IC50: 0.55 M), six ciprofloxacin-sulfonamide hybrids (3f, 5d, 7a, 7d, 7e, and 9b) had strong inhibitory efficacy against DNA topoisomerase IV, with an IC_{50} range of 0.23-0.44 μM. Five ciprofloxacin-sulfonamide hybrids (3f, 5d, 5e, 7a, and 7d) with IC_{50} ranges of 0.43-1.1 μM (IC50 of ciprofloxacin: 0.83 μM) also effectively inhibited

DNA gyrase. Compounds 3a and 3b demonstrated a notable improvement in antibacterial activity over ciprofloxacin against both Gram-positive and Gram-negative pathogens, namely Staphylococcus aureus and Escherichia coli. Their respective MIC values were 0.324 and 0.422 μM, which is 4.2-fold and 3.2-fold lower than ciprofloxacin (MIC = 1.359 μM). Additionally, as compared to ciprofloxacin, the most effective compounds had fewer convulsive and CNS adverse effects and concurrently reduced GABA expression. (29)

CONCLUSION

In the early phases of acute infections, when bacteria are rapidly proliferating, sulfonamides are most effective. They have no effect on germs that are dormant. Bacteriostatic effects can be obtained by using sulfonamide alone, albeit usually there is some lag time before they become apparent. The reason for this is that bacteria must eat stored folic acids, folinic acid, purines, thymidine, and amino acids. The bactericidal effects of potentiated sulfonamides are more pronounced at high concentrations, such as those seen in the urine. This bactericidal effect, however, is time-sensitive. In either scenario, having sufficient humoral and cellular defense systems is essential for effective infection eradication. The only currently known inhibitors of this enzyme are sulfa medications, although new, promising small-molecule alternatives are on the horizon. Although these medications are thought to be a safer option, research on them is still in its early stages. Excess PABA, folic acid, thymine, purine, methionine, plasma, blood, albumin, tissue autolysates, and endogenous protein-degradation products can significantly impair the effectiveness of sulfonamides.

For the purpose of predicting the biological effects of chemical compounds based on mathematical and statistical relationships, quantitative structure-activity relationship (QSAR) approaches are crucial. Based on the molecular characteristics of diverse substances, quantitative structure-property relationship (QSPR) techniques estimate the physiochemical attributes. These ligand-based computational screening methods offer a cost- and labor-effective replacement for laboratory-based screening procedures. Here, we first go over the background of QSAR, the various QSAR kinds, and the key procedures for building and validating QSAR models. QSAR methods aid in the selection of hits from a huge chemical library. The hit molecules may be bought and their activity can be tested in tests. Promising therapeutic candidates can be created by further optimizing the compounds with shown activity. Thus, QSAR investigations eliminate the synthesis and testing of several compounds, saving a significant amount of time and money.

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