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Synthetic Approaches, Biological Activity Evaluations, and Mechanistic Investigations of Sulfaguanidine-Linked Molecules

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Abstract

Because of its importance in medicinal chemistry, scientists have been interested in linking sulfaguanidine to different heterocycles to develop potential bioactive candidates. To accomplish this, four approaches have been adopted. The adopted approaches included condensation with electrophilic reactants, coupling with nucleophilic aromatics and active methylene compounds, click cycloaddition, and multicomponent reaction. This review reports all the adopted synthetic approaches, the biological activities studied, and the mechanistic investigations of the reported organic sulfaguanidine-linked molecules throughout 2015-2024.

Keywords: Sulfaguanidine; Antimicrobial; Mechanistic Investigations; Sulfonamides; Synthetic Approaches.

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List of Abbreviations

Serial	Abbreviation	Full Description
1.	µM	Micromole
2.	Å	Angstrom
3.	AChE	Acetylcholinesterase
4.	Arg	Arginine
5.	Asp	Aspartic Acid
6.	ATCC	American Type Culture Collection

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Serial	Abbreviation	Full Description
7.	CA	Carbonic Anhydrase
8.	CAIs	Carbonic Anhydrase Inhibitors
9.	Casp	Caspase
10.	CDK-9	Cyclin-Dependent Kinase 9
11.	DBSA	*p*-dodecylbenzenesulfonic acid
12.	DMF/DMA	Dimethylformamide Dimethyl acetal
13.	DNA	Deoxyribonucleic Acid
14.	DPPH	2,2-Diphenyl-1-picrylhydrazyl
15.	EGFR	Epidermal Growth Factor Receptor
16.	Glu	Glutamic Acid
17.	Gly	Glycine
18.	hCA	Human Carbonic Anhydrase
19.	HCT-116	Human colon cancer cell line
20.	HepG-2	Human liver cancer cell line
21.	Ile	Isoleucine
22.	IZ	Inhibition Zone
23.	K_I	The Inhibitory Constant
24.	LC_{50}	Lethal Concentration 50%
25.	Leu	Leucine
26.	Lys	Lysine
27.	MCF-7	Michigan Cancer Foundation Breast cancer Cells
28.	MDA-MB231	M D Anderson Metastatic Breast Cancer Cells
29.	MIC	Minimum inhibitory concentration
30.	mL	Milliliter
31.	MMP-2	Matrix Metalloproteinase-2
32.	nM	Nanomole
33.	RNCS	Alkyl isocyanates
34.	RNCS	Alkyl isothiocyanates
35.	Ser	Serine
36.	SGN	Sulfaguanidine
37.	SI	Selectivity Index
38.	Thr	Threonine
39.	TK	Tyrosine Kinase
40.	VEGFR	Vascular Endothelial Growth Factor

1. Introduction

Sulfaguanidine (**SGN-01**)is a sulfonamide-derived bacteriostatic agent that was prepared for the first time by Marshall and colleagues in 1940[1–3].It has long been used for the management of dysentery based on the fact that it has a bad absorption propertiesfrom the gastrointestinal tract [4, 5]. **SGN-01** has a sulfonamide group attached *para*to an amin group on benzene ring[6]. Several sulfaguanidine-linkedbioorganic molecules have been developed over the last decade [2, 7–10]. **SGN-01** has been reported as a vital fragment in the construction of bioorganic molecules such as, anticancer [7, 11, 12], anti-inflammatory [13], antidiabetic [14, 15], antimicrobial [2, 16, 17], antiviral [18, 19], and carbonic anhydrase inhibitors (CAIs) (**Figure 1**) [20–22]. The effectiveness of sulfaguanidines in targeting Methicillin-Resistant *Staphylococcus aureus* has also been reported [9, 23].

Several approaches have been documented in the construction of sulfaguanidine-linked derivatives. The majority of these approaches considered the nucleophilic nature of the aniline fragment of both scaffolds[24–28]. So, sulfaguanidine were condensed with electrophilic reactants like carboxylic acid and acid derivatives[29], sulfonyl chlorides[1], and aryl halides [24, 28, 30, 31]. Another approach intended the transformation of the nucleophilic nature of the primary amine groups of both scaffolds into electrophilic centers through diazotization [32–34] and the resulting electrophiles subsequently treated with nucleophilic reactants rather than electrophilic[29, 35, 36].The produced diazonium salts undergone coupling with nucleophilic aromatic amines, active methylene compounds like dimethyl oxalate, ethyl cyanoacetate, acetylacetone, or malononitrile(**Figure 1**) [37, 38].

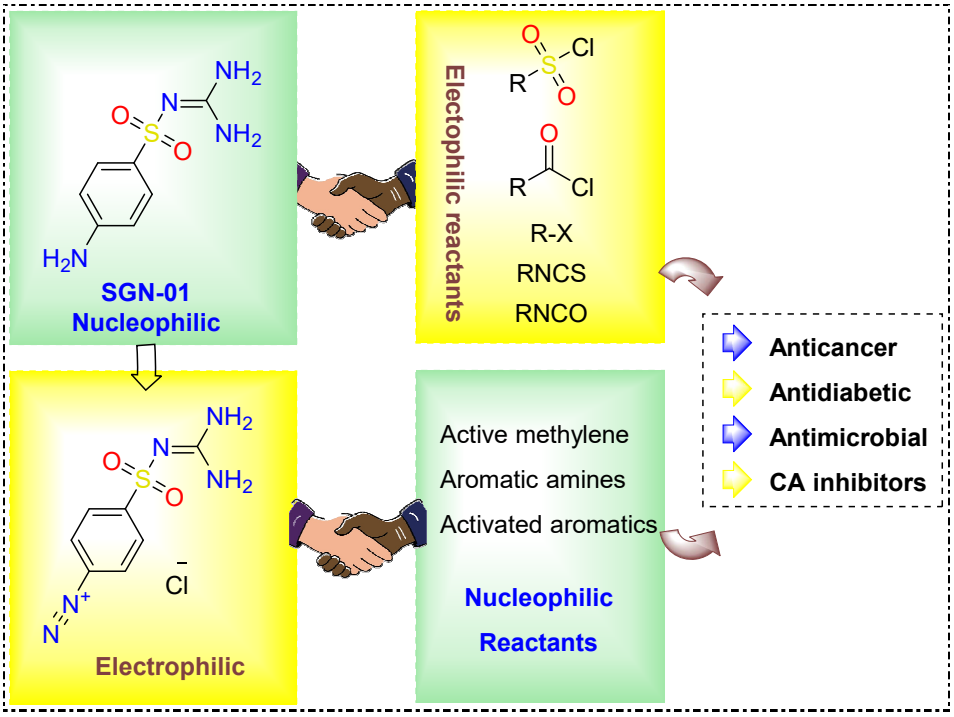

Figure 1: Summary of synthetic approaches and biological activities sulfaguanidines

Diazonium salts of sulfaguanidine have also been utilized for the construction of diverse heterocycles like pyrazoles and pyridines through the reaction with active methylene compounds followed by binucleophiles [37, 39, 40]. A third approach for the development of sulfaguanidine-linked molecules considered the conjugation of this molecular fragment with well-known medications [41, 42]. The conjugation of sulfaguanidine with the well-known antibiotic ciprofloxacin is an example of this last approach. This aims to boost the activity of the early medication and/or to reduce its unwanted effect [42]. The sulfaguanidine-ciprofloxacin hybrid has been documented to diminish the mortality rate and lessen the epileptic side effects of ciprofloxacin alone [9, 43]. One last approach contemplated replacing of the oxazines' oxygen with the nitrogen of the amine functionality of sulfaguanidine [44–46].

1.1. Preparation of sulfaguanidine

Sulfaguanidine has several synonymic names, including sulfoguaniland sulfoguanyl, can be prepared in an environment-friendly method, as shown in **Figure 2,** by stirring acetanilide with sulfonyl chloride to obtain *N*-acetylsulfanilyl chloride[47]. The addition of an equimolar amount of guanidine nitrate followed by deacetylation gives sulfaguanidine[48, 49].

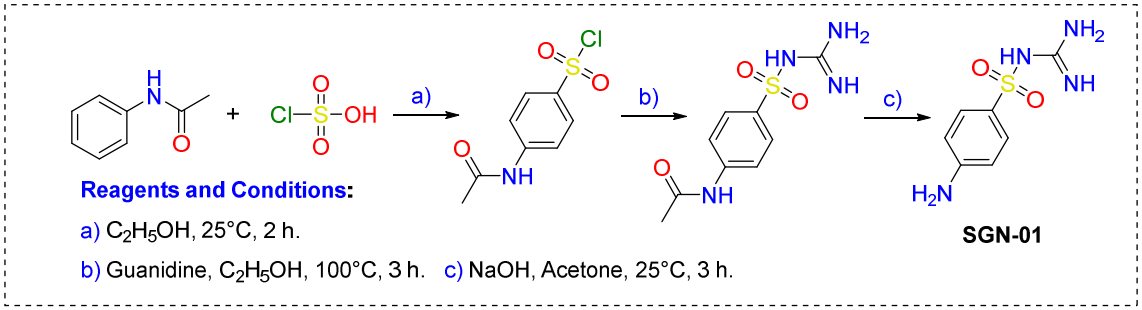

Figure 2: Preparation of sulfaguanidine (SGN-01).

2. Literature survey

In continuation to my contribution to the scientific research community[50–68], over the next few pages, the adopted synthetic approaches, and the studied activities together with the potential mechanistic pathways (whenever reported) of the sulfaguanidine-linked bioorganic molecules who had developed from 2015 to 2024 will be discussed. They will be classified based on the studied activity.

2.1. Sulfaguanidine-linked antimicrobial candidates

In the past year, a cooperation of Egyptian and Saudi researchers has developed nineteen 7-methoxyquinolines linked to benzenesulfonamide moieties by the nucleophilic displacement of the chloro substituent of 4-chloro-7-methoxyquinoline with different sulfa drugs (**Figure 3**). All the synthesized compounds were investigated for their antimicrobial activity against six pathogenic microbes. The screened microbes included four Gram-positive & Gram-negative bacteria (*E. coli, P. aeruginosa, S. aureus, and B. subtilis)* and two fungi (*C. albicans and C. neoformans).* Results revealed that compound **SGN-02** has a noteworthy effect on most tested bacterial and fungal strains. The MICs of **SGN-02**against *E. coli,* and *P. aeruginosa* were 62.50 and 250.00 µg/mL, respectively compared with 250 and 500 µg/mL for the reference antimicrobial drug amoxicillin/clavulanic acid. The MIC values for *S. aureus and C. albicans were* 125.00 µg/mL for each pathogen compared with 250.00 µg/mL and 125.00 µg/mL for the reference antimicrobials amoxicillin/clavulanic acid and Nystatin [69].

Sulfaguanidine got clenched with *p*-nitrobenzoyl chloride and the obtained amides were reduced and subsequently used as starting materials for the development ofnovel sulfonamides (**Figure 3**).The compounds obtainedhave demonstrated antimicrobial activity against Gram-positive bacteria (*Bacillus cereus* and *B. subtilis*), Gram-negative bacteria (*Enterobacter aerogenes*), clinical isolate,and mold. Particularly, compound **SGN-03** showed the highest activity against *B. subtilis* with an inhibition zone of 14.00 mm at a concentration of100 µg/disc. Compounds **SGN-04** and **SGN-05**showed antibacterial activity against *B. cereus* and *E. aerogenes* with IZ diameters of 10.00 mm for each ata concentration of100 µg/disc. Only the *para*-bromo derivative **SGN-03**has shown a weak antibacterial activity against Gram-negative bacteria *L. pneumophila.* The same derivative was found active toward the studied fugal strains *C. tropicalis*, *S. cerevisiae, and A. fumigatus*[1].

A set of malononitrile-based benzenesulfonamides were synthesized by condensation of sulfaguanidine and analogous sulfonamides with triethyl orthoformate and malononitrile (**Figure 3**). The produced compounds were assessed for their antioxidant and antimicrobial activities. At a concentration of 1 µM, the malononitrile linked **SGN-06** displayed a mild inhibition in the DPPH free radical scavenging assay. **SGN-06** also exhibited mild activities as antibacterial against *P. aeruginosa, S. aureus, and B. subtilis* with a percentage inhibition range of 12.40% - 32.71%. No activity has been detected against *C. albicans*[70].

2.2. Sulfaguanidine-linked anticancer candidates

Two sets of pyrazolones linked with sulfaguanidine have been recently reported. The amine functionality of sulfaguanidine was first diazotized and then treated with either malononitrile or diethyl oxalate. The obtained dinitrile and diester were subjected to a set of binucleophilic cycloaddition reactions(**Figure 4**)[71]. The final compounds were evaluated for their potential cytotoxicity on hepatocellular, colorectal, and breast cancer cell lines. Additionally, they have been evaluated as CDK-9 inhibitors. The diaminopyrazole-linked sulfaguanidine derivative **SGN-07** showed an outstanding cytotoxic effect toward the investigated cancer cells with IC_{50} values of 6.57 µM, 9.54 µM, and 7.97 µM, respectively. It inhibited the effect of CDK-9 with an IC_{50} value of 0.16 µM [7]. The docking experiment (**Figure 5**) of **SGN-07** uncovered its effective binding interaction with four amino acid residues (Ile25, Lys48, Glu66, and Asp109). In this interaction pattern, the sulfaguanidine fragment played a significant role.

Researchers who conducted the previous study have extended their work to enhance the ADMET properties of the prepared compounds. They decreased the number of hydrogen bond donor and acceptor groups [72] by replacing diethyl oxalate with ethyl acetoacetate, and replacing malononitrile with ethyl cyanoacetate to produce **SGN-08**(**Figure 4**)[73]. **SGN-08**exhibited a greater tumor uptake (27.3%) compared to ^{131}I-labelled **SGN-07** (17.2%). Among the obtained entities, **SGN-08**significantly arrested the growth of MCF-7 and potently inhibited CDK-9 with an IC_{50} value of 0.496 µM. Cell cycle analysis of the breast

cancer cells MCF-7 evidenced the capability of the aminopyrazolone-linked sulfaguanidine **SGN-08**to arrest the cell cycle of at the G2/M phase with coincident apoptotic effect. Analyzing the *in silico* binding mode of **SGN-08**displayed two hydrogen bonding interactions with Asp104 and Asp109 within connection distances of 3.05 Å and 3.00 Å (**Figure 5**). In this interaction pattern, the sulfaguanidine fragment has also played a significant role.

A group of Middle East researchers has developed a novel triazolyl quinazolinediones by the reaction of different enaminones with substituted quinazolinedione reactants (**Figure 4**). The cytotoxic activity of the synthesized compounds was evaluated against two human carcinomas: colorectal carcinoma (HCT-116) and hepatocellular carcinoma (HEP-G2). Some compounds showed significant potency with variant degrees compared with staurosporin. The quinazoline derivative **SGN-09** with phenyltriazine substituent at position 6 displayed the best activity as cytotoxic against the human hepatocellular carcinoma (HEP-G2) with an IC_{50} value of 2.68 µM, which is about 2.6 folds higher than that of staurosporin (IC_{50} 7.18 μM) [74].

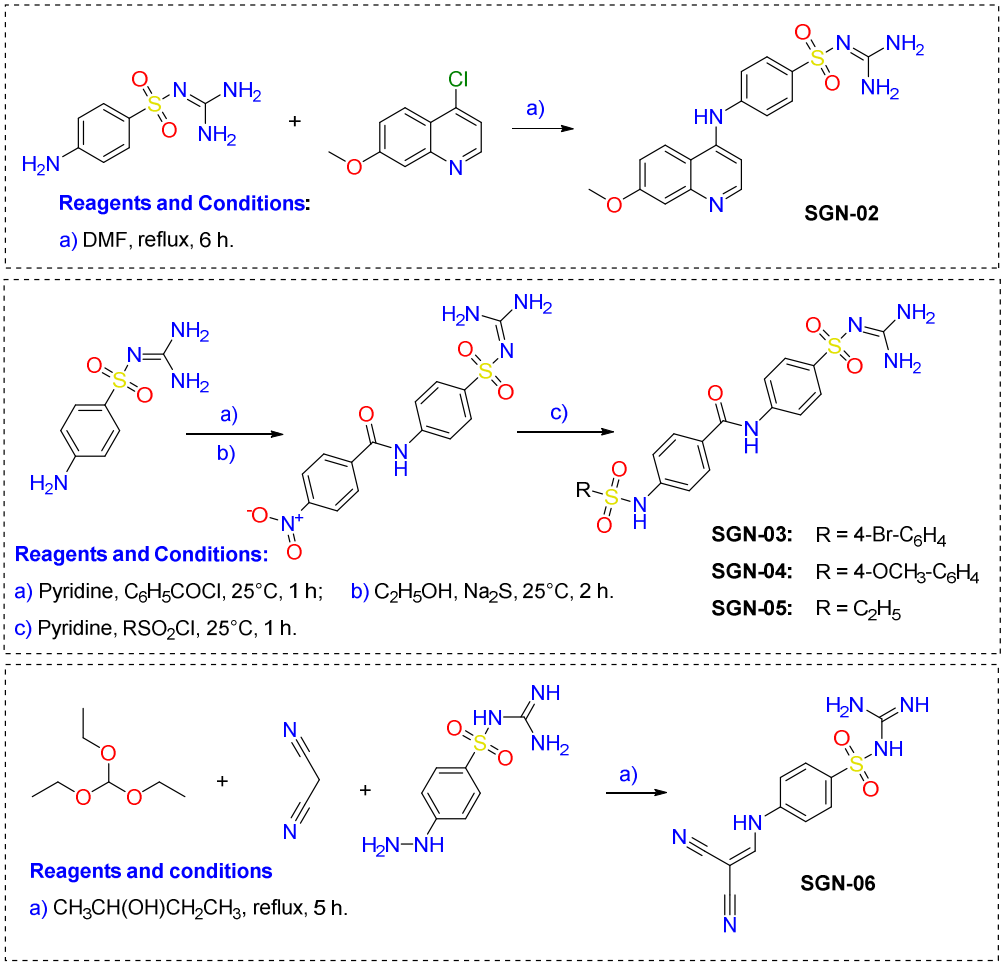

Figure 3: Adopted synthetic approaches for the synthesis of **SGNs 02-06**

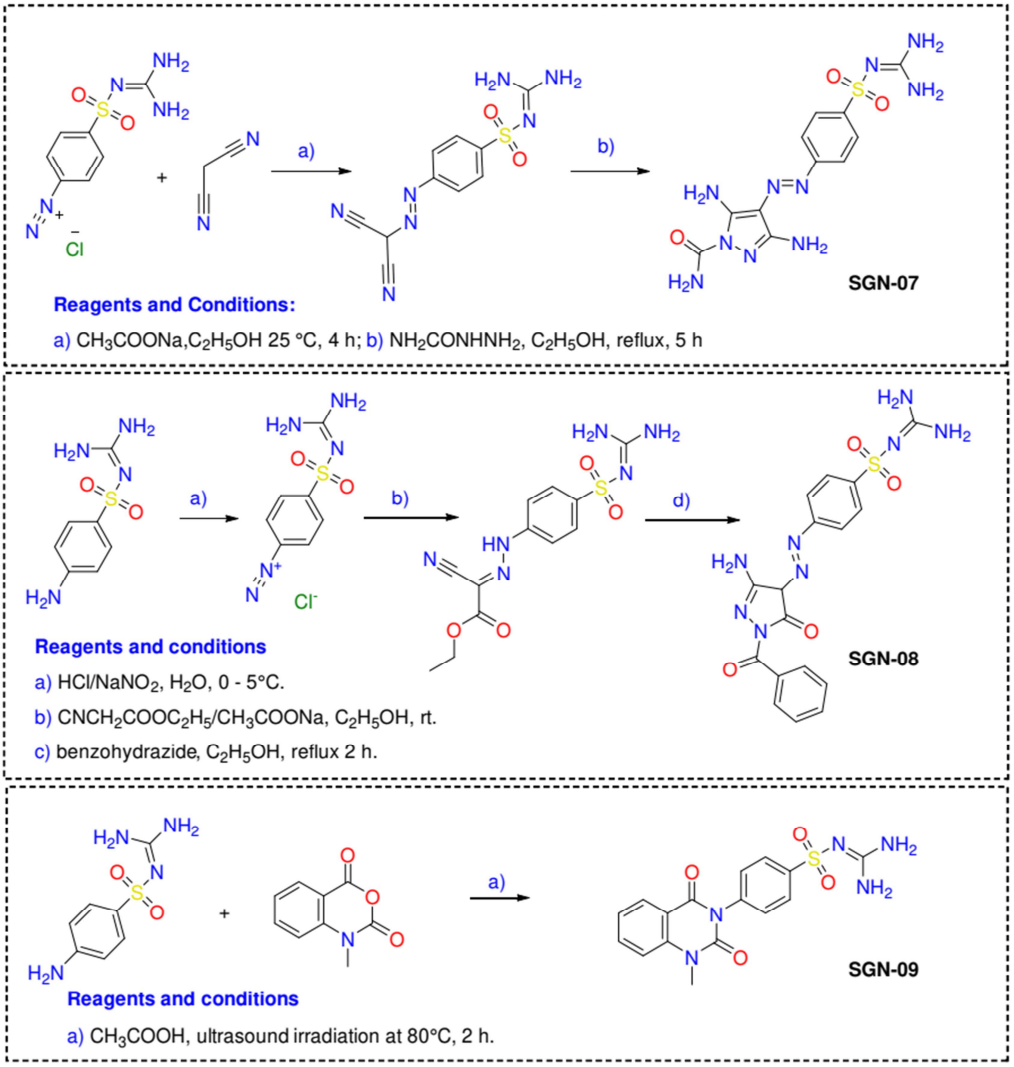

Figure 4: Adopted synthetic approaches for the synthesis of SGNs 07-09

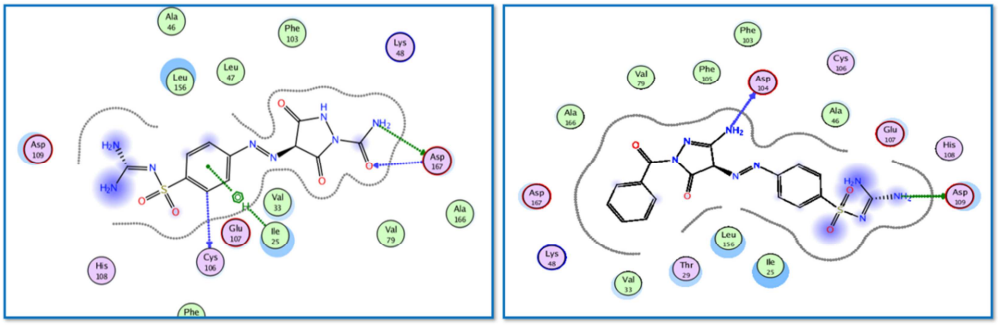

Figure 5: Connection patterns of **SGN-07** (left) and **SGN-08** (right) with CDK-9

In 2017, numerous pyridazine-linked sulfaguanidines were synthesized and screened for their *in vitro* cytotoxic activity on HCT-116 and MCF-7. Target compounds were synthesized by reacting 4-((6-((3-aminophenyl)amino)pyridazin-3-yl)amino)-*N*-carbamimidoylbenzenesulfonamide with a set of alkylisothiocyanates RNCS. Also, they were tested *in vivo* against Ehrlich ascites carcinoma (EAC) in mice. The *in vitro* VEGFR inhibition assay was conducted at a dose of 10.00 µM. Results revealed the capability of the *N*-allylthiouria derivative **SGN-10**(**Figure 6**) to disrupt HCT-116 and MCF-7 cells with IC_{50}

values of 30.30 µM and 27.50. µM, respectively. It also exhibited the best inhibition power in the VEGFR kinase assay (92.20%) [24, 75].

In 2016, Elzamly*et al.* prepared plenty of pyrazolo[4,3-*d*]pyridazines by refluxing 4-chloro-3,7-diphenyl-1*H*-pyrazolo[3,4-*d*]pyridazine with sulfaguanidine and other sulfonamides in glacial acetic acid to get **SGN-11-SGN-14**(**Figure 6**)and many other analogs. Some selected candidates were evaluated as cytotoxicin HCT-116 (colon cancer). Among the prepared series, the compounds with hydrazine side chain instead of the sulfaguanidine fragments have showed higher toxicities towards the colorectal carcinoma cell line even that they were more efficient than the standard drug Imatinib [31].

Two years ago, the concomitant inhibition of MMP-2, CA II, and VEGFR-2 under the effect of a set of 1,2,4-triazole hybrids linked to various sulfonamide pharmacophores was investigated (**Figure 6**)[76]. The microwave-assisted click cycloaddition reaction was utilized to connect various alkynyltriazoles with the diazotized benzensulfonamides. All the synthesized adducts were evaluated for their anticancer actions against the colon cancer cells (Caco-2), breast cancer cells (MDA-MB-231), and hepatocellular carcinoma (HepG-2). Their potential to promote the expression of the p53 and to induce apoptosis were also investigated. The safety of the prepared adducts was assessed as well on one normal human cell (Wi-38). The 1,2,4-triazole hybrid **SGN-15** was among the most effective compounds that show IC_{50} values at the nanomolar scale (10.42, 11.96, and 9.85 nM towards Caco-2, MDA-MB-231, and HepG-2, respectively). Compound **SGN-15** significantly participated in the overexpression of p53 in the tested cell lines (2.47 folds in Caco-2, 1.38 folds in MDA-MB-231, and 3.18 in HepG-2 compared to negative control). The mechanistic evaluation of **SGN-15** proved that it inhibits MMP-2 (IC_{50} = 20.26 nM), CA II (IC_{50} = 187.50 nM), and VEGFR-2 (IC_{50} = 21.00 nM), while the reference MMP-2, CA II, and VEGFR-2 inhibitors quercetin, and sorafenib showed IC_{50} values of 299.50 nM, 27.30, and 4.92 nM, respectively. The same sulfaguanidine derivative induced apoptosis in the hepatocellular carcinoma cells in the early stage (from 0.31% to 2.61%) and late stage (from 0.12% to 7.49%). It also showed a high level of selectivity (SI ≈ 3.5). Docking studies suggested the binding patterns of **SGN-15**with the specified biological targets [76]. The sulfaguanidine fragment of the new compound participated in the interaction with critical amino acid residues in MMP-2 (Thr143, Leu137, and Ser151), CA II (Thr199, Thr200, and Zn262), and VEGFR-2 (Cys919 and Gly922) (**Figure 7**).

The same group of researchers who conducted the previous investigation have also adopted a similar procedure to develop another set of 1,2,3-triazole linked to terminal sulfonamide moieties (**Figure 8**). The synthesized molecules were evaluated for their cytotoxic effect against three cancer cells (MCF-7, HCT-116, and HepG-2) and for their inhibitory profile against EGFR TK. The benzothiazole derivative **SGN-16** showed cytotoxic activity with IC_{50} values of 34.30, 7.52, and 17.57 nM while the isatin derivative displayed IC_{50} values of 33.50, 17.40, and 91.04 nM against MCF-7, HCT-116, and HepG-2, respectively. As well, the sulfaguanidine liked 1,2,3-triazole **SGN-16** and **SGN-17** showed potent EGFR TK inhibition activity at nanomolar concentrations (413.30 nM and 468.21 nM) [77].

A series of thienopyrimidine-sulfonamides hybrids (**Figure 8**) was developed in 2023 as suggested anticancer and apoptotic inducers. This series was obtained by reacting ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate or diethyl 3-methylthiophene-2,4-dicarboxylate with formamide followed by getting the produced pyrimidone derivatives chlorinated with phosphorus oxychloride and finally replacing the chloro substituents with the amine functionality of the appropriate sulfonamide. Their cytotoxic effect was investigated on human breast cancer cells (MCF-7 and MDA-MB231) and the results were compared to Doxorubicin. The effects of the new sulfaguanidine hybrids on FGFR-1, Caspase-3, and apoptosis were also studied. The sulfaguanidine derivatives **SGN-19** and **SGN-18** exhibited moderate activities against both studied cells. The IC_{50} values of **SGN-19** were 35.79 and 40.17 µM while those of **SGN-18** were 6.17and 8.68 µM, respectively. Their selectivity indices were found to be greater than Doxorubicin (SI = 12.79 and 44.86 compared with 1.75 for MCF-7; SI = 11.40 and 31.90 compared with 1.27 for MDA-MB231). The IC_{50} values of **SGN-19** and **SGN-18** on FGFR-1 131.95 and 325.65 µM, respectively compared with 53.09 µM for Doxorubicin. both compounds and the positive equally induced Caspase-3 activity in MDA-MB-231 cells. The molecular docking experiment of **SGN-18** suggested that the sulfa guanidine fragment is participating in the binding with four amino acid residues of FGFR-1 (Glu253, Arg212, Thr255, and Thr214) (**Figure 9**) [78, 79].

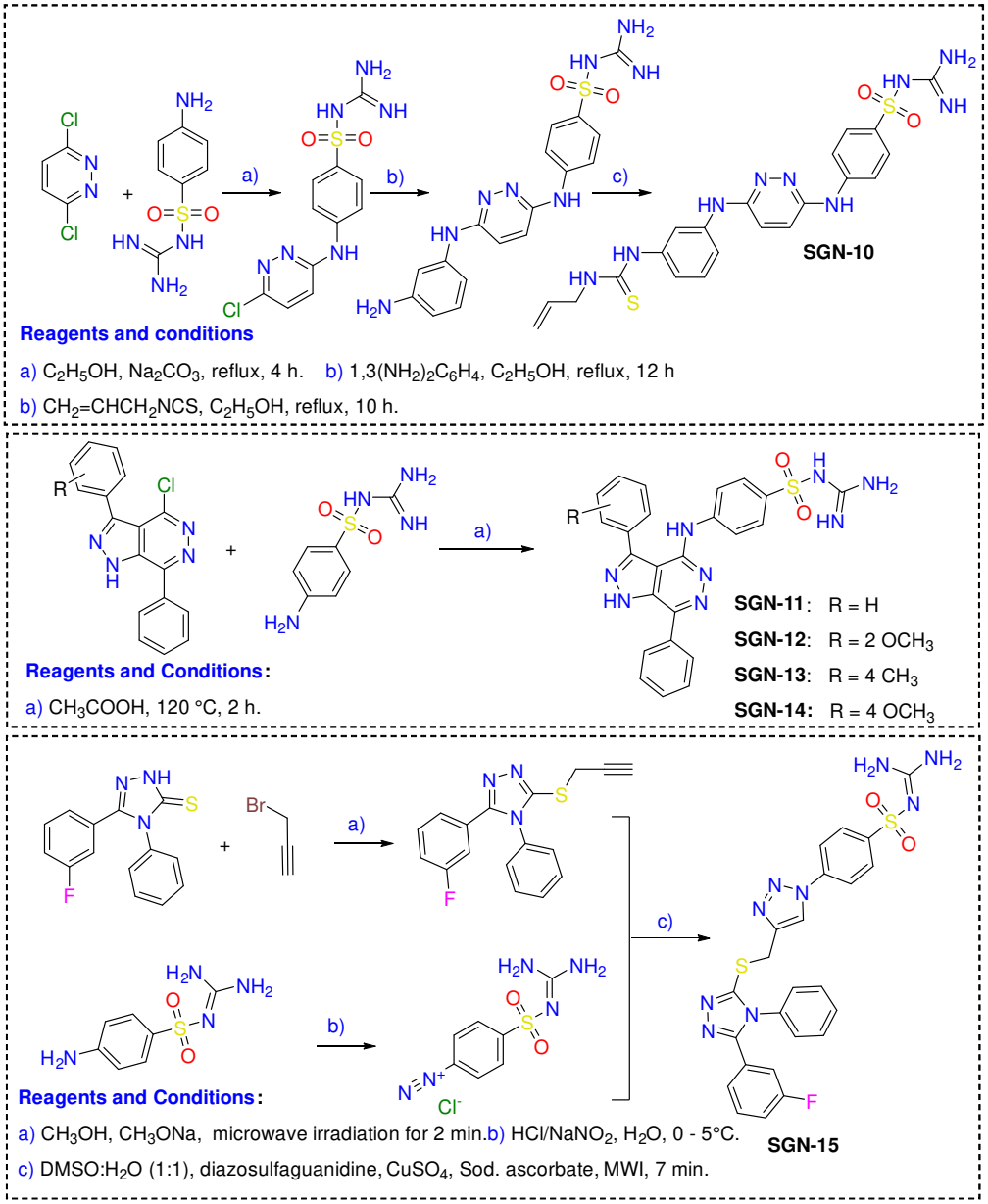

Figure 6: Adopted synthetic approaches for the synthesis of SGNs 10-15

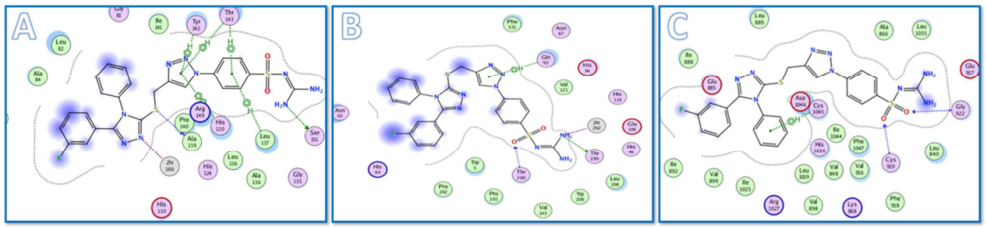

Figure 7: 3D binding modes of **SGN-15** with A) MMP-2 , B) CA II, and C) VEGFR-2 [76].

2.3. Sulfaguanidine-linked antidiabetic candidates

The drug-drug hybridization approach has recently been used to develop eight paracetamol-linked sulfonamides through azo (-N=N-) linkers (**Figure 10**). The developed compounds were suggested to have antidiabetic activity mediated by α-amylase, and α-glucosidase inhibition effect. This was achieved by getting *p*-aminophenol acetylated with acetic anhydride while the

appropriate sulfonamide converted to their diazo analogs. Coupling of the resulting N-acetyl paracetamol and diazo compound furnished hybrid molecules of paracetamol linked through diazo linkers with sulfaguanidine and other analogous sulfonamides [80]. The designed diazo-paracetamols were screened for their *in vitro* inhibitory effect on α-amylase and α-glucosidase. The results proved moderate to potent activity. Among the diazo-paracetamols studied, **SGN-20** was identified as weak inhibitor with IC_{50} value of 22.66 µM and 96.52 µM compared to Acarbose IC_{50} = 0.43 µM and 1.24, respectively. Assessment of the virtual binding of the designed hybrids with α-amylase and α-glucosidase showed that the sulfaguanidine adduct has the highest binding energies [80].

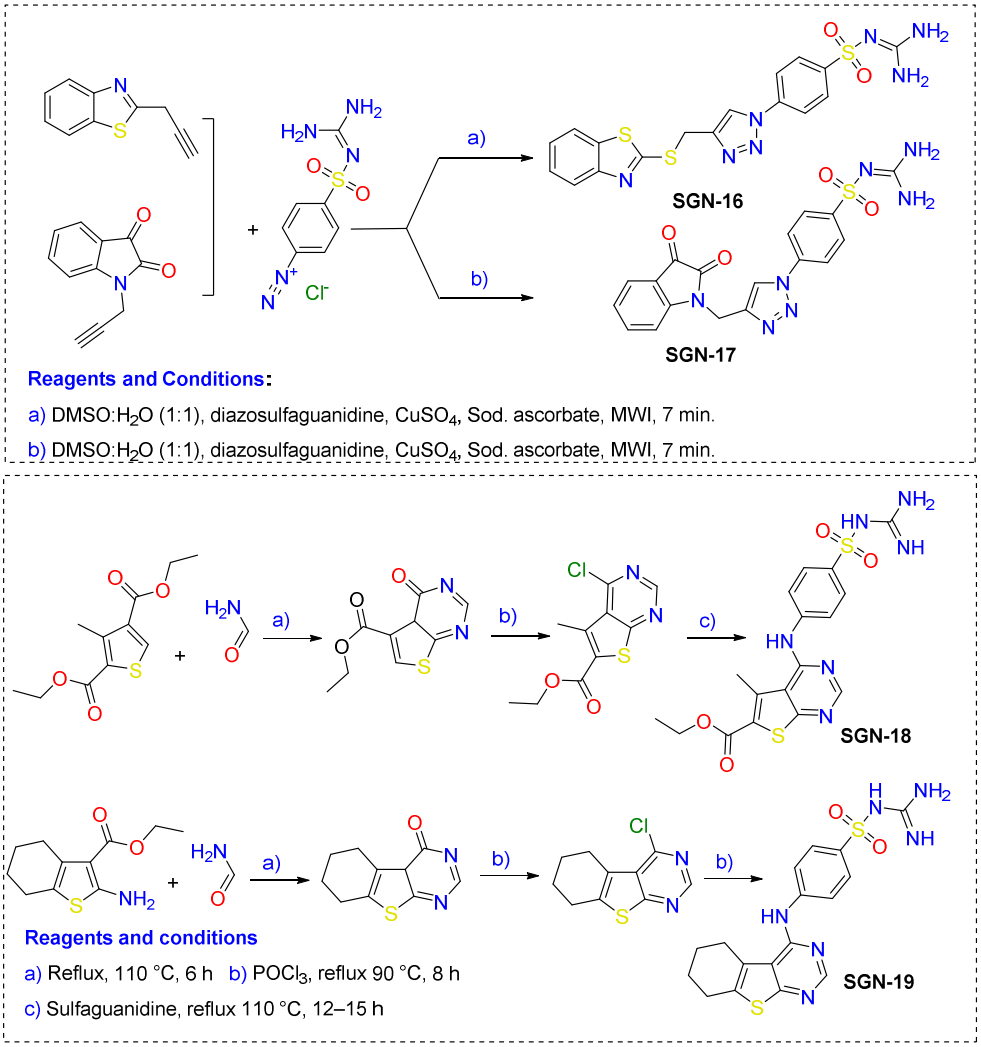

Figure 8: Adopted synthetic approaches for the synthesis of SGNs 16-19

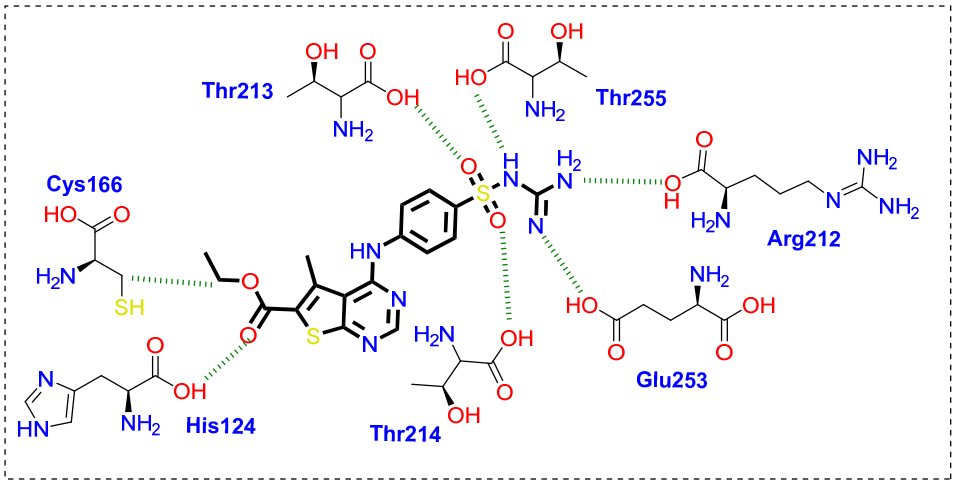

Figure 9: binding interaction of **SGN-18** with FGFR-1[78].

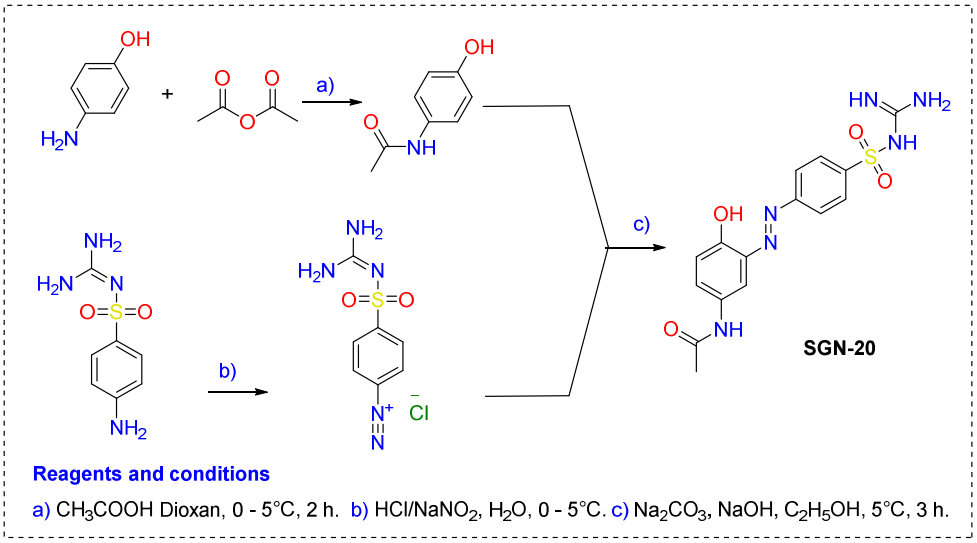

Figure 10: Adopted synthetic approach for the synthesis of SGN-20

2.4. Sulfaguanidine-linked carbonic anhydrase inhibitor candidates

Applying three-components reaction, novel sulfaguanidines linked to acridine moieties (**Figure 11**) were synthesized by a group of Turkish researchers as suggested carbonic anhydrase inhibitors. Sulfaguanidine, cyclohexane-1,3-dione (2 moles), and aromatic aldehydes were allowed to react in an aquatic environment at room temperature in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as catalyst. The synthesized compounds were evaluated for their abilities to inhibit two isoforms of the human carbonic anhydrases (*h*CA I and*h*CA II), and the obtained results were compared to that of acetazolamide as apositive control. The synthesized compounds were identified as moderate inhibitors of both isoforms with IC_{50} values at a micromolar concentration range(118.40-257.50 µM for *h*CA I and 86.70-249.40 µM for *h*CA II).Among these, **SGN-21** showed the strongest inhibition potential on the isoform I (IC_{50} = 118.40 µM) while **SGN-22** was the most effective on the isoform II (IC_{50} value 86.70 µM)[81].

AbdelGawad *et al.* designed a series of 4-(thiazol-2-ylamino)-benzenesulfonamides(**Figure 11**) and evaluated them for their cytotoxic activity on human breast cancer cell line MCF-7 and for their carbonic anhydrase inhibitory effect. Among the developed entities, the sulfaguanidine derivative **SGN-23**showed a good profile as a cytotoxic (IC_{50} = 11.90 µM) and excellently inhibited all the examined isoforms (CA I, II and IX) K*i* values of 0.85 nM, 0.53nM, and 8.50nM, respectively[36, 82].

In 2020, A Turkish team has developed a series of sulfonamides linked toprop-1-en-1-ylbenzamides as suggested inhibitors of the human carbonic anhydrase isoforms I and II. This was rendered reality through allowing glycine to condense with benzoyl chloride followed by cyclization of the produced benzoylglycine with *p*-methoxybenzaldehyde and finally treating the produced xazol-5(4*H*)-one with a variety of sulfonamides. Results of the *In vitro* enzyme assays showed that the

sulfaguanidine derivative **SGN-24** significantly inhibited the isoforms hCA I and hCA II as well as the human AChE with K*i* values of 17.62 nM, 18.67 nM, and 10.60 nM, respectively [83]. The reference compound acetazolamide displayed relatively lower activities towards the *h*CA I and *h*CA II (Ki = 30.74 and 22.27 nM) [83–85].

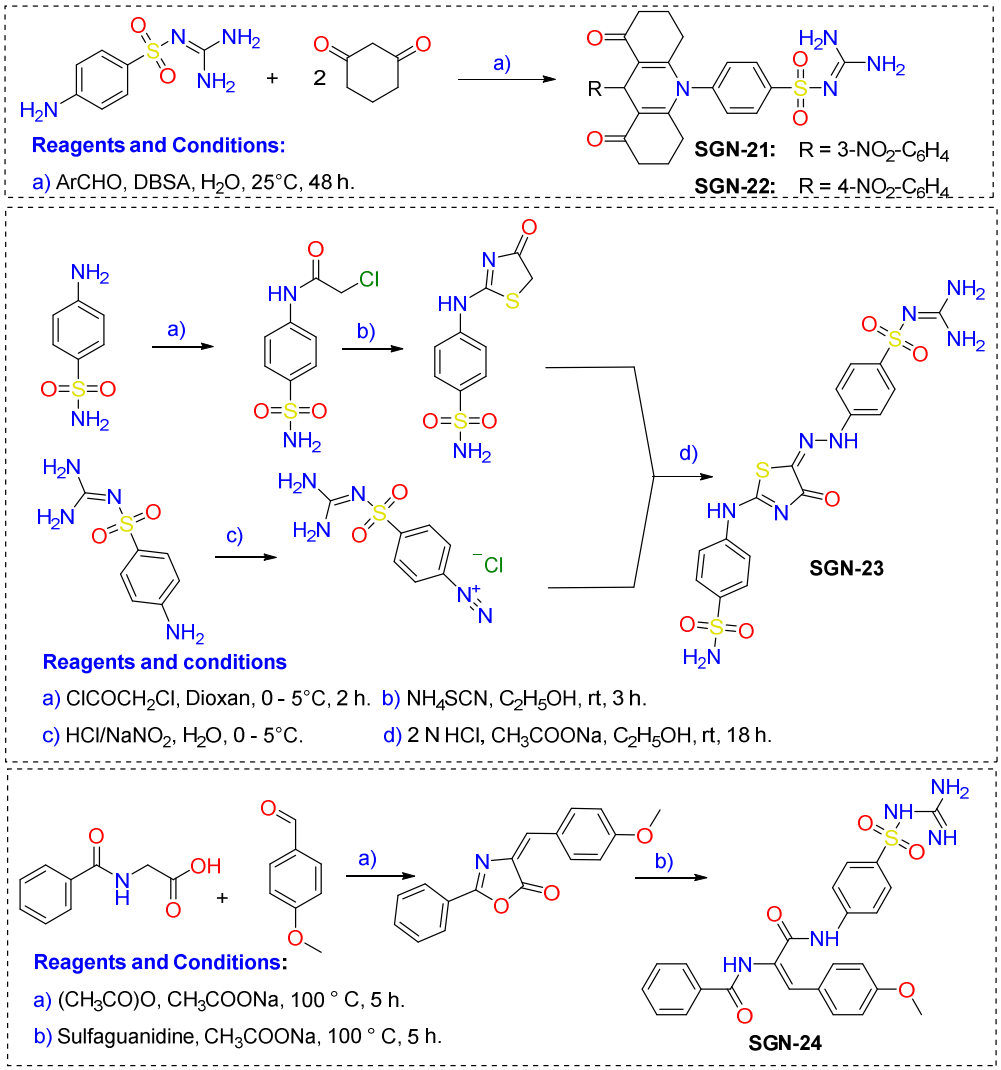

Figure 11: Adopted synthetic approaches for the synthesis of SGNs 21-24

3. Mechanistic investigations of sulfaguanidine-linked molecules

AS shown earlier, literatures scan shows four major biological activities for the reported sulfaguanidine-linked molecules over the past ten years. These include anticancer, antimicrobial, antidiabetic, and carbonic anhydrase inhibition.

Regarding the anticancer assessments, thirteen molecules (**SGN-07-SGN-19**) have been reported as potent cytotoxic against several cancer cell lines. These cells include hepatocellular (HCT-116 & HEP-G2), colorectal (HCT-116 & Caco-2), and breast cancer cell lines (MCF-7 & MDA-MB-231). Out of the active cytotoxic sulfaguanidine-linked molecules, seven candidates were investigated for their potential mechanistic effect (**SGNs 07, 08, 10, 15, 16, 17,** and **18**) .**SGN-07** inhibited the effect of CDK-9 with an IC_{50} value of 0.16 µM [7]. The docking experiment of **SGN-07** suggested the effective binding interaction of this compound with four amino acid residues (Ile25, Lys48, Glu66, and Asp109). The aminopyrazolone-linked **SGN-08** potently inhibited CDK-9 with an IC_{50} value of 0.496 µM and arrested the cell cycle of MCF-7 at the G2/M phase [72, 86]. The computational study of **SGN-08** displayed its capability to make two hydrogen bonds with Asp104 and Asp109. **SGN-10** exhibited good inhibition power in the VEGFR kinase assay (92.20%) [24]. The 1,2,4-triazole hybrid **SGN-15** was among the most effective compounds as an inhibitor of MMP-2 (IC_{50} = 20.26 nM), CA II (IC_{50} = 187.50 nM), and VEGFR-2 (IC_{50} = 21.00 nM) [76]. Also,it promoted the expression of the p53 (2.47 folds in Caco-2, 1.38 folds in MDA-MB-231, and 3.18 in HepG-2) and induced apoptosis in the investigated cancer cells. The sulfaguanidine fragment of this compound has contributed to the formation of a number of the interaction with critical amino acid residues in MMP-2 (Thr143, Leu137, and

Ser151), CA II (Thr199, Thr200, and Zn262), and VEGFR-2 (Cys919 and Gly922) [76]. The sulfaguanidine liked 1,2,3-triazole **SGN-16** and **SGN-17** have showed potent EGFR TK inhibition activity at nanomolar concentrations (413.30 nM and 468.21 nM) [77]. The IC_{50} value of **SGN-18** on FGFR-1 was 325.65 μM. The molecular docking experiment of this derivative uncovered the participation of its sulfaguanidine fragment to the binding with four amino acid residues of FGFR-1 (Glu253, Arg212, Thr255, and Thr214) [57, 78].

Regarding the antimicrobial screening, five molecules (**SGN-02-SGN-06**) showed noteworthy effects against several Gram-positive & Gram-negative and fungal pathogens (*E. coli, P. aeruginosa, S. aureus, B. subtilis, B. cereus*, *E. aerogenes, C. albicans and C. neoformans, C. tropicalis*, *S. cerevisiae, and A. fumigatus)* as proves by their inhibition zones and MICs. The potential mechanistic effects of these antimicrobial compounds include the inhibition of DNA replication, the inhibition of DNA gyrase and topoisomerase activities, the inhibition of protein biosynthesis, and the inhibition of cell wall biosynthesis [87, 88]. However, literatures that reported these compounds did not specified any potential mechanistic effects for the synthesized compounds [1, 69, 70].

Regarding the antidiabetic activity investigation, only one molecule (**SGN-20**) has been reported as potent antidiabetic. This antidiabetic candidate was investigated for their potential mechanistic effect on α-amylase and α-glucosidase.**SGN-20** was identified as a weak inhibitor with IC_{50} values of 22.66 μM and 96.52 μM, respectively. Assessment of the virtual binding α-amylase and α-glucosidase showed that it has showed relatively high binding energies [80].

Four SGNs have been reported as CA inhibitors (**SGNs-21, 22, 23, and 24**). **SGN-21** displayed an IC_{50} value of 118.40 μM on the isoform I while **SGN-22** was effective against the isoform II with anIC_{50} value of 86.70 μM) [81].**SGN-23** excellently inhibited the isoforms I, II and IXwith K*i* values of 0.85 nM, 0.53 nM, and 8.50 nM, respectively [36].**SGN-24** significantly inhibited the isoforms hCA I and hCA II with K*i* values of 17.62 nM and 18.67 nM, respectively [83].

4. Conclusion

This review presents a comprehensive survey of synthetic strategies and reported biological activities as well as the mechanistic investigations of sulfaguanidine as a vital molecular scaffold in the development of drug candidates. This molecular scaffold has proven its advantages as a potent fragment in the skeletons of active bioorganic molecules targeting diverse biological targets in the field of chemotherapeutics, antimicrobials, and antidiabetics. Their efficacies in developing selective inhibitors of a specific isoform of carbonic anhydrase have also been reported. The diverse roles that sulfaguanidines undertaken in synthesizing biologically active candidates targeting vital enzymes collectively underscore their values as efficient fragments in designing drug candidates.

5. Future perspectives

The encouraging results of several SGNs highlighted here emphasize the importance of this scaffold in Medicinal Chemistry. Molecules incorporating **SGN-01,** especially **SGN-16,** showed significant anticancer potential against MCF-7, HCT-116, and HepG-2 human carcinomas. The sulfaguanidine linked 1,2,3-triazole **SGN-16** has also been identified as a potent cytotoxic against MCF-7, HCT-116, and HepG-2 cells with IC_{50} values of 34.30, 7.52, and 17.57 nM.**SGN-16**was found to be effective as EGFR TK inhibitors. Also, sulfaguanidine-linked compounds have shown significant CA inhibitory potential. Efficiently, the thiazole-linked sulfaguanidine derivative **SGN-23** showed a good profile as CA inhibitor on isoforms I, II and IX with K*i* values of 0.85 nM, 0.53 nM, and 8.50 nM, respectively. The investigation of this compound revealed that its prominent activity may be attributed to the presence of sulfaguanidine moiety that can effectively form hydrogen bonds with critical amino acid residues in the specified biological targets. Accordingly, it warrants complementary structural optimization and further research efforts which may further enhance its activity as anticancer and CA inhibitors.

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