Triazine Moiety as cancer inhibitor drugs

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Abstract

One of the most notable structures in heterocyclic chemistry, the 1,3,5-triazine (s-triazine) scaffold, has been discovered to have a broad range of applications in biological activity with its use greatly present in the field of anticancer drugs research and development. This review will tackle the aspect of formulation, synthesis and significance of s-triazine derivatives to alleviate cancer. Sub-stitution is multi-directional because their more precisely symmetrical aromatic solution permits tri-, di-, and mono-substituted analogues to be made with greater selectivity and efficiency. Having been indicated as being the mode of action as the inhibitors of the key cancer targets such as DNA topoisomerases, phosphatidylinositol 3-kinase (PI3K) mammalian target of rapamycin (mTOR), focal adhesion kinase (FaK) and the carbonic anhydrase (CA) isoforms. The derivatives have been found to possess great cytotoxicity and improved inhibition property than conventional drugs on a large number of cancer cell lines. These types of structure-activity relationship (SAR) studies have also helped in optimization of the compounds in order to attain higher potency, selectivity and bioavailability. Despite the known limitations, e.g., off-target effects and pharmacokinetic limitations, the scaffold has received discovery of new compounds, e.g., gedatolisib and ZSTK474, or bimiralisib which have emerged in clinical testing which further reflect the promise in the therapeutic implications of the scaffold. The 1,3,5- triazine scaffold, typically provides a versatile effective framework which can be utilized to uncover the next generation of anticancer complexes in a reasonable and efficient manner.

1. INTRODUCTION

Ring compounds with one or more different ring atoms—that is, atoms other than carbon, such as N, O, S, or P—are known as heterocycles. The most significant heterocyclic systems are compounds with five or six members[1].The synthesis of heterocyclic compounds containing nitrogen has garnered increased attention due to its high binding affinity and usefulness for a variety of biological receptors[2].Triazine-containing substances, especially 1,3,5-triazines, have drawn a lot of interest because of their diverse biological properties, which include anticancer activity against a variety of targets[3], [4], [5], antimalarial[2], [6], [7], antileshmanial[8] and antiinflammatory[9][10]. 1,3,5-triazines, also known as s-triazines, are a well-known family of chemicals that continue to attract a lot of attention because of their numerous uses in various industries, such as the manufacturing of herbicides and polymer photostabilizers[11]. With three carbons swapped out for nitrogens, the triazine structure is a heterocyclic ring analogue of the six-membered benzene ring. The isomers of triazine are known as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine and are differentiated from one another by the locations of their nitrogen atoms[2].

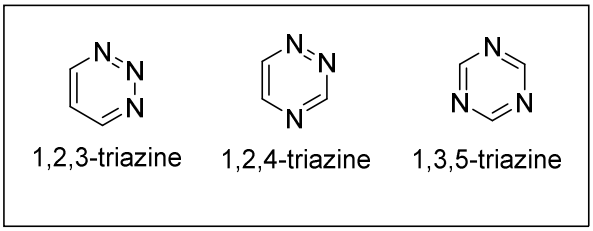

Fig. 1. Various isomers of triazine

Because of its unique structure and electronic properties, 1,3,5-triazine (s-triazine) has been utilised extensively in chemical processes that provide access to a wide range of beneficial compounds. The reason for the increased interest in this scaffold is the temperature-controlled reactivity of the chlorine atoms at positions 2, 4, and 6, which enables the sequential insertion of different substitutes to make mono-, di-, and tri-substituted triazines[12][13].

It is simple to create sophisticated s-triazine derivatives using the inexpensive and easily accessible cyanuric chloride (2,4,6-trichloro-1,3,5-triazine)[14], [15], [16], [17]. Numerous 1,3,5-triazine derivatives are produced when chloride ions are substituted in cyanuric chloride, and these tiny molecules have been studied as physiologically active[18], [19], [20], [21].Human African Trypanosomasis can be treated using s-triazine derivatives of polyamines, whose action is mostly reliant on the triazine moiety[22].

2. ANTICANCER ACTIVITY

1,3,5-triazine is a symmetrical heterocyclic aromatic ring that allows the structure to expand in many vectors. Research over decades has identified a variety of characteristics of s-triazine derivatives[23]. The leading cause of mortality worldwide is tumours. Lung cancer (2.1 million new cases and 1.8 million deaths), breast cancer (million new cases and 880,000 deaths), prostate cancer (1.3 million new cases and 360 thousand deaths), and stomach cancer (1 million new cases and 783 thousand deaths) had the highest cancer mortality rates in 2018[24]. It is now feasible to identify the most effective target for targeted therapy because to decades of study that has produced more accurate descriptions of the mechanisms occurring in cancer cells.

The creation of tiny molecules comes in second and is just as significant. The creation of chemical compounds based on a structural-activity relationship (SAR) has led to the development of more potent, selective, and less cytotoxic medications. 1,3,5-triazine, a symmetrical heterocyclic aromatic ring that permits multi-vector structure expansion, is the main linker. Numerous characteristics of s-triazine derivatives have been discovered during decades of investigation[25].

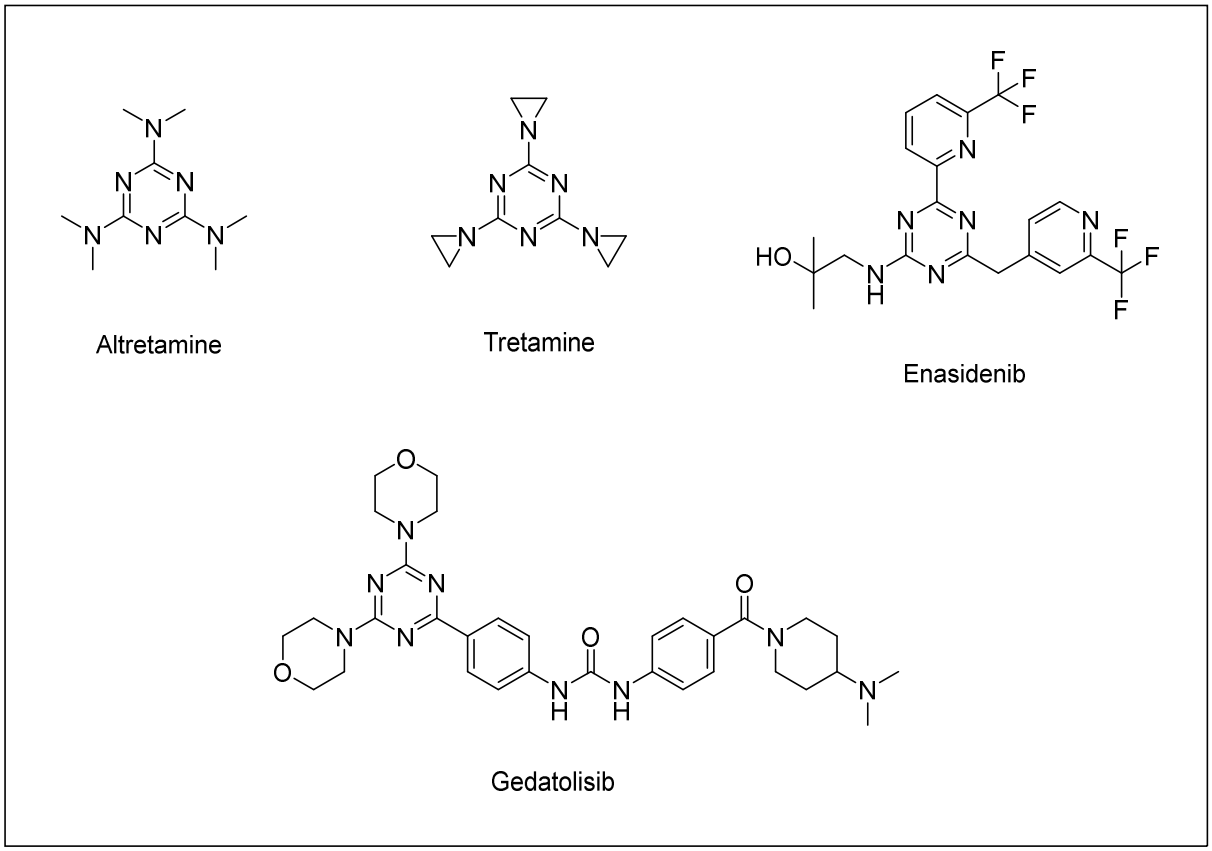

Fig. 2. Drugs containing triazine ring

S-triazines' structure-activity relationships (SARs) demonstrated that they might be used as templates to create new medications for cancer treatment. According to the structure of the protein kinases' active region, tri-substituted s-triazine derivatives primarily inhibit heat shock protein 90, phosphatidylinositol-3-kinase, epidermal growth factor receptor, and NADP+-dependent isocitrate dehydrogenases, whereas di-substituted s-triazine derivatives primarily inhibit topoisomerase, Bruton's tyrosine kinase, focal adhesion kinase, and cyclin-dependent kinases. Furthermore, the triazine moiety's six-membered nitrogen-containing basic heterocycles, including morpholine, piperidine, and piperazine, were advantageous for its antitumor action[26].

2.1 TOPOISOMERASE INHIBITION

Numerous DNA topoisomerase inhibitors have been documented in recent years for use in both basic and therapeutic settings. Wang et al. made the initial discovery of topoisomerase in E. coli in 1971. Since then, research on the structure, role, and mechanism of topoisomerase has been undertaken. Type I and type II topoisomerases are the two broad categories into which human DNA topoisomerases are often divided. Without ATP, type I topoisomerases can create a covalent phospho tyrosyl bond that causes transitory single-strand breaks (SSBs) in DNA molecules. The big homodimeric proteins known as type II topoisomerases, on the other hand, need ATP for full catalytic activity and have the potential to cause temporary DNA double-strand breaks (DSBs)[27]. Topoisomerases are therefore crucial for a number of cellular functions, including transcription, chromosomal segregation, replication, and segregation. As a result, topoisomerases provide excellent targets for anticancer medication development. Based on how they block DNA, human DNA topoisomerase inhibitors may be divided into two groups: topoisomerase poisons and topoisomerase catalytic inhibitors[28].

Most clinical anticancer drugs, such as doxorubicin, etoposide, mitoxantrone, salvicine, and teniposide, are classified as topoisomerase poisons. These drugs work by stabilising covalent topo-DNA complexes and turning this enzyme into a cellular toxin, which kills cancer cells. By preventing topoisomerase's vital enzymatic function, topoisomerase catalytic inhibitors can destroy tumour cells. Catalytic inhibitors include a variety of structurally varied chemicals that either block the enzyme on the ATP-binding site (purine analogues), inhibit DNA cleavage (merbarone), or inhibit ATP hydrolysis (bisdioxipiperazine analogues). A panel of chemical agents with a variety of architectures has resulted from rigorous attempts to investigate effective tumour therapies due to the widespread participation of topoisomerase in association with different carcinomas[29].

A kind of ATP-competitive catalytic topoisomerase II inhibitor 1 with the core 9H-purine scaffold was described by the Novartis research group in 2009[30] then, utilising a virtual screening technique, Perdih et al. discovered that 1,3,5-triazines monocyclically replaced the

compounds' 9H-purine motif. With IC_{50} values in the micromolar range (IC_{50} = 229 M), 4-amino-6-(phenylamino)-1,3,5-triazines (a) demonstrated strong topoisomerase IIa inhibitory action in the hit selection. Additionally, compound (a) demonstrated cytotoxicity against normal HUVEC cells (IC_{50} = 122 M), MCF-7 (IC50 = 129.0 M), and HepG2 cell lines (IC50 = 20.53 M). Additionally, a set of 4,6-disubstituted-1,3,5-triazin-2(1H)-one analogues was created by Perdih et al[31][32]. Relevant structure-activity relationship (SAR) information on the function of substituents added at position 6 of the 1,3,5-triazin-2(1H)-one core was given by this study. With an enhanced IC_{50} of 57.6uM, 6-(benzylthio)-4-((3-chlorobenzyl)thio)-1,3,5-triazin-2(1H)-one was shown to be a topoisomerase II inhibitor. These substances, however, demonstrated little cytotoxicity to cancer cells. The 1,3,5-triazin-2(1H)-one scaffold's substituents at position 4 are further optimised by Perdih et al. to increase the inhibitory efficacy that would exhibit action at the cellular level. The most effective compounds IC_{50} values of 8.1uM and 11.1uM, respectively, following virtual screening and experimental assessment for human topo IIa inhibition. They were also superior to the positive medication etoposide (IC_{50} = 28.6 uM). Furthermore, compound (b) IC_{50} values of 38.7 M demonstrated superior HepG2 cell inhibitory efficacy[33].

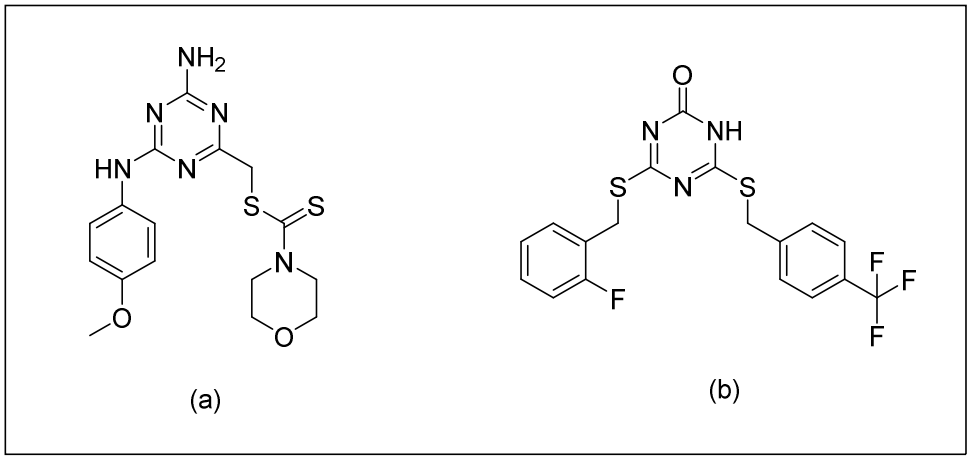

Fig. 3. Topoisomerase II inhibitors

2.2 PHOSPHOIONOSITIDE 3 KINASE INHIBITOR

A key component in the PI3K/Akt/mTOR signalling cascade, phosphatidylinositol 3-kinase (PI3K) is a lipid kinase. Based on the kind of catalytic structural domain, the most extensively

researched type I PI3Ks are further separated into class IA (PI3K,α, β, and δ) and class IB (PI3Kγ). Because of its critical role in cell growth and survival, blocking the PI3K/AKT/mTOR pathway has gained widespread recognition as an appealing cancer treatment approach. There are several PI3K inhibitors being studied at the moment, such as isoform-specific PI3K inhibitors, pan-PI3K-mTOR inhibitors, and pan-class I PI3K inhibitors. Derivatives of dimorpholino-substituted s-triazine have demonstrated significant promise in the treatment of PI3K-related malignancies. Clinical studies are presently underway for a number of intriguing candidates, including gedatolisib, bimiralisib, and ZSTK474[34].

Another dimorpholino-substituted s-triazine derivative created by Pfizer, gedatolisib (PKI-587), is undergoing a phase III clinical study as a possible therapy for HER2-negative breast cancer, hormone receptor-positive breast cancer, and acute myeloid leukaemia. Gedatolisib has strong anticancer effects in an in vivo xenograft model and strong inhibitory efficacy against both PI3K and mTOR in vitro. Its poor selectivity over various PI3K isozymes, however, may result in off-target effects and lessen its therapeutic usefulness. Furthermore, gedatolisib needs to be injected, which makes it a potentially impractical medication for cancer patients. Therefore, it is preferable to structurally alter gedatolisib in order to create PI3K and mTOR inhibitors with improved isozyme selectivity and metabolic stability.

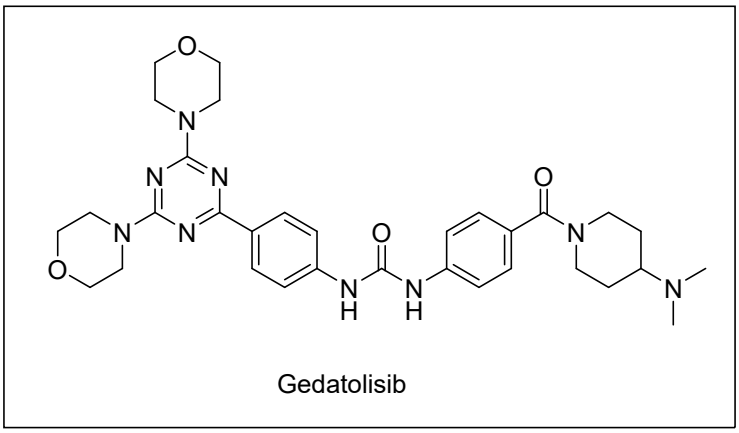

Fig. 4. Gedatolisib drug

Bis-morpholino s-triazine-based compounds have been identified by the Venkatesan group as strong dual PI3K/mTOR inhibitors[35].

Gedatolisib's poor permeability, low log p, and high molecular weight could potentially be the cause of its inadequate plasma levels when taken orally. To decrease molecular weight and raise log p, a single morpholine group in gedatolisib produced a number of monomorpholino 1,3,5-triazine derivatives, which Mansour et al. reported were substituted with 3-oxa-8-aza-bicyclo(3.2.1)octane[36]. Pharmacokinetic analyses revealed a half-life (>60min) and high oral bioavailability in naked mice following oral treatment (10 mg/kg). According to metabolite assessment investigations, the bridged-morpholine group's ethylene bridge served as the primary site of metabolism and was identified as its metabolite structure. Consequently, a dual PI3K/mTOR inhibitor that works well when taken orally[37]. An s-triazine derivative called ZSTK474 was chosen by Zenyaku Kogyo along with over 1500 other analogues[38]. With IC_{50} values of 16, 44, 5, and 49 nM for PI3Kα, β, δ, and γ, respectively, ZSTK474 strongly inhibits all four PI3K isoforms, indicating that it is a pan-PI3K inhibitor[39]. Unfortunately, ZSTK-474's resistance and on-target/off-tumor side effects have forced its withdrawal from clinical studies. Consequently, ZSTK-474's structure must be improved in order to enhance its PI3K-specific targeting[40].

As seen in Figure 5, D. Ross et al. investigated compound 1 by substituting piperazine for a single morpholine group in ZSTK474, which they used as a lead compound. Compound 1 demonstrated a >70-fold decrease in PI3Kβ (IC_{50} = 1093 nM) and PI3Kγ (IC_{50} = 1873 nM) inhibition and a 36-fold decrease in PI3Kα (IC_{50} = 180 nM) and PI3Kδ (IC_{50} = 142 nM) inhibition, demonstrating the importance of oxygen replacement in this area.

PI3K isoform inhibition (IC_{50} = 2.9 21 nM) was comparable to ZSTK474 (IC_{50} = 3.9 20.8 nM) when compound 1 was N-acetylated to yield compound 2. Bifunctional inhibitors demonstrated nanomolar inhibition towards PI3K (IC_{50} = 130 nM and 107 nM, respectively) and PI3Kδ (IC_{50}= 236 nM and 137 nM, respectively) and low micromolar inhibition for PI3Kβ and PI3Kγ (IC_{50}= 1.5 3.9 uM) in enzymatic inhibition assays. This was done in order to further explore the role of the morpholine oxygen in these compounds on PI3K inhibition[41]. Compound capacity to

suppress downstream AKT and ERK1/2 phosphorylation allowed it to exhibit greater anti-proliferative capabilities in three tumor-derived cell lines (A375, D54, and SET-2). In 2011, Shepherd and colleagues discovered that adding a methoxy group to ZST474's 2-(difluoromethyl)-1H-benzo[d]imidazol at position 4 might improve its interaction with the PI3K enzyme[29]. In light of this, Hou et al. created a novel 1,3,5-triazine derivative that contains semicarbazones as novel possible PI3K inhibitors, further substitutes piperazine for one morpholine groups[42]. Compound 3 had outstanding inhibitory efficacy against PI3Kα, with an IC_{50} value of 0.32 nM, according to additional study. However, in the intragastric delivery of the U87-MG human glioblastoma xenograft model test, compound 3 demonstrated comparable anticancer activity at 20 mg/kg/day in contrast to ZSTK-474's 40 mg/kg/day in vivo antitumor effectiveness. Compound 3’s pharmacokinetic characteristics remain suboptimal, nevertheless, thus more structural modification of the substance is required to enhance its physicochemical characteristics[40].

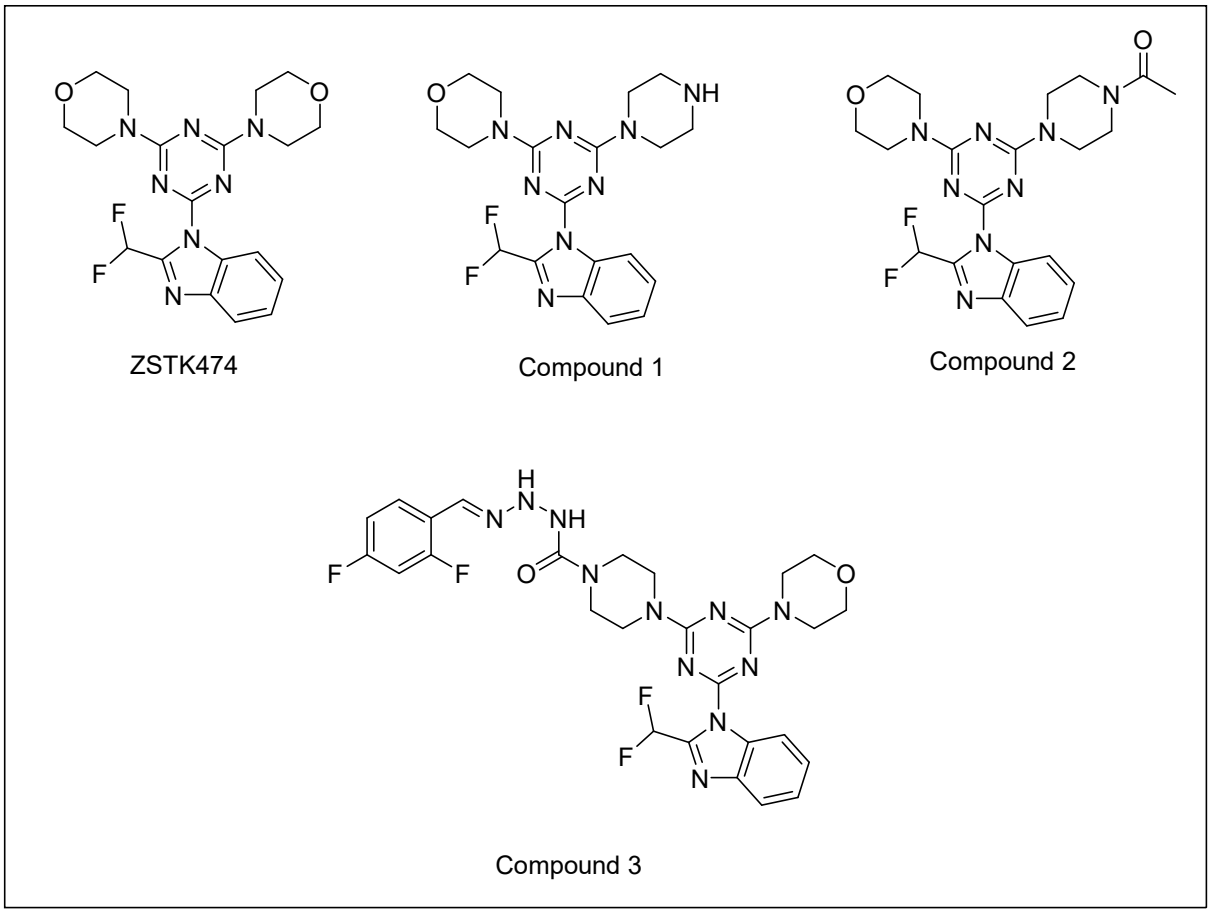

Fig. 5. Phosphoionisitide 3 kinase inhibitors

Although BKM120 is one of the most sophisticated pan-PI3K inhibitors available for clinical use, it disrupts microtubule polymerisation in an off-target manner. Wymann et al. have determined that it varies from BKM120 in that it has a single atom that may be divided into distinct PI3K and tubulin activities[43]. Bimiralisib (1) was created by substituting s-triazine for the BKM120 core, which was originally inspired by ZSTK474 and BKM120. The goal was to minimise microtubule interactions and increase chemical solubility and bioavailability. Compound 1 demonstrated strong inhibition against pan-PI3K and no microtubule-destabilizing agent action, as predicted[44]. Among all, compound 1 is a very selective pan-PI3K inhibitor that targets mTOR kinase in a balanced manner. It has cleared phase I investigations and is currently being studied in phase II trials for advanced solid tumours and relapsed and refractory lymphoma[45], [46].

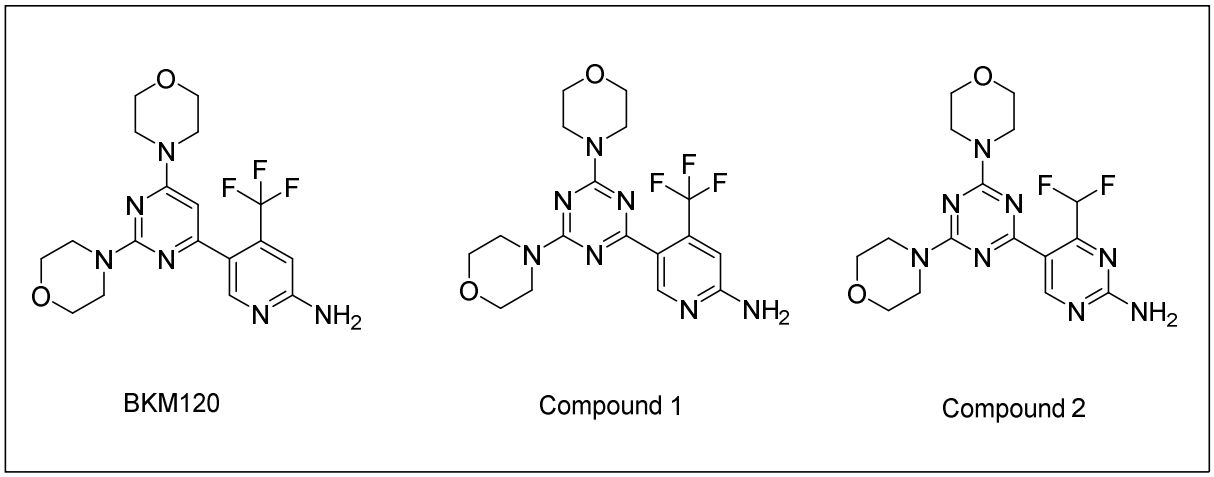

Fig. 6. BKM120 and its derivatives

In a mouse xenograft model, compound 2 exhibited strong anticancer action at a dose nearly eight times reduced than the original phase-II inhibitor, while having a low nano molar affinity for PI3Kα (IC_{50} = 2.2 nM)[47]. They recently created a number of strong covalent PI3K inhibitors, beginning with lead compound 2, by focussing on solvent-exposed cysteines that are more than 10 Å away from an ATP-site-directed central group[48]. Several compounds with an acrylamide warhead and various linker modules were created in order to evaluate the necessary warhead reactivity as well as the Michael acceptor's spatial trajectory. In rat liver microsomes, compound 2 exhibited the highest PI3Kα enzyme inhibitory activity (IC_{50} = 1 nM) and superior stability among these compounds[49].

2.3 FOCAL ADHESION KINSAE INHIBITION

A cytoplasmic tyrosine kinase weighing 125 kDa is called focal adhesion kinase (FAK). One important factor in the development of tumours is the dysregulation of FAK-dependent functions such cell adhesion, proliferation, survival, and motility. Apoptosis is inhibited and the frequency of metastatic tumours rises when FAK is overexpressed[50]. Compound 1 (Figure 7) is the most potent FAK inhibitor, according to Dao et al. (IC_{50} = 0.05 μM). In comparison to TAE 226 (0.19

μM, 0.23 μM, 1.9 μM, and 0.26 μM), compound 26 demonstrated growth inhibitory action on human glioblastoma (U-87MG), human colon cancer (HCT-116), MDA-MB-231, and human prostate cancer (PC-3). The findings were 0.42 μM, 0.13 μM, 0.14 μM, and 0.63 μM. Additionally, compound 1 demonstrated a good fit by molecular docking into the FAK's ATP binding site[51].

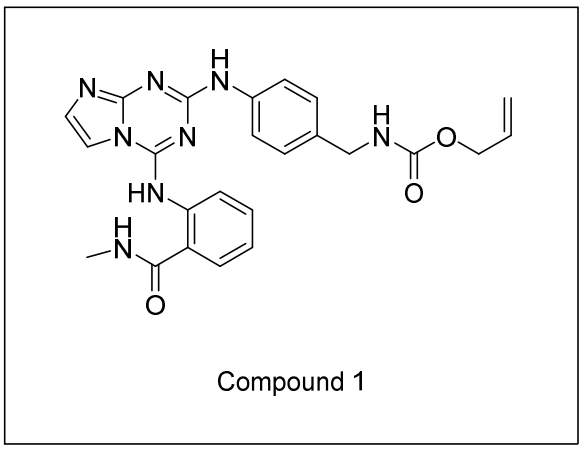

Fig. 7. FAK inhibitor

2.4 CARBONIC ANHYDRASE INHIBITORS

The metalloenzymes from the lyase group known as carbonic anhydrases (CAs) are in charge of maintaining pH equilibrium and catalysing the reversible process that forms the bicarbonate ion HCO3 from carbon dioxide and water[52]. We can identify the common variations CAI and CA II in mammals among the several isoforms. Enhanced levels of CA IX and CA XII is seen in pathological conditions like hypoxia. These enzyme types have a role in ion transport, intercellular communication, and pH homeostasis regulation. 2-[4-Chloro-5-methyl-2(naphthalen-1-ylmethylthio)-benzenesulfonyl]-1-[4-chloro-6-(4-sulfamoylphenylamino)-1,3,5-triazin-2-ylamino]guanidine acted with strongest selectivity toward hCA IX versus hCAI (hCAI/hCAIX=18) and hCAII (hCAII/hCAIX=4). HeLa cancer cells were significantly

cytotoxically affected by compound 1 (IC_{50}=17uM), however non-cancerous HaCaT cells were not harmed (IC_{50}=61uM).

Havránková et al.'s study examined how CA I, II, and IX interacted with 1,3,5-triazine derivatives that included sulfonamide, piperazine, and amino alcohol. The findings demonstrated that the greatest ratio of selective inhibition (hCAIX/hCAII) was attained by 1,3,5-triazines with a 4-hydroxyaniline substituent: compound 2 (18.50)[53].

New 1,3,5-triazine derivative were created based on the structure of SCL-0111 (Figure 4), and their capacity to inhibit CA I, II, IX, and XII was examined. With a KI value of 0.91nM, one compound showed the most promising selective inhibition of CA IX, whereas other compound showed a KI value of 14.6nM[54].

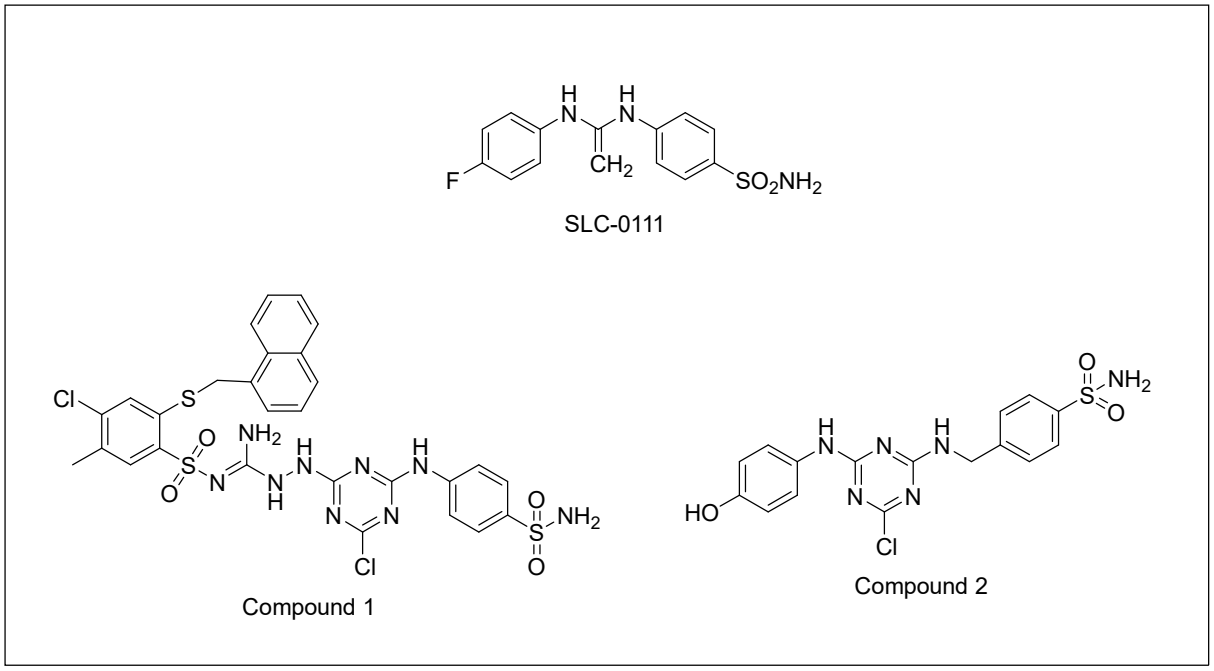

Fig. 8. Carbonic anhydrase inhibitors

3. CONCLUSION

Using that type of 1,3,5-triazine scaffold has been made multi-faceted and high possibility of being utilized in formation of anticancer agents since it has structural versatility and broad biological activities. s-Triazine products are highly active to inhibit the major cancer targets through the intersection of topoisomerase II, PI3K / mTOR, FAK and types of carbonic anhydrase isoforms. Rational design More effective and specific compounds of improved pharmacokinetics, have been created based on large research programs of structure-activity relationships (SAR). Examples of chemicals that have been found to be promising during preclinical and clinical trials include gedatolisib, ZSTK474 and bimiralisib. Enhanced optimization however necessitates the need of other alterations in order to change isozyme selectivity, lower off-target activities and oral bioavailability. In conclusion, the Ancillary TS 1, 3, 5 triazineric- derivatives constitute a key chemotype in search of anticancer agents and this poses a great opportunity during search of safe, as well as more effective targeted chemotherapies.

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