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s-Triazine: A Versatile Scaffold in Drug Design and Therapeutics

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Abstract
s-Triazine serves as a versatile scaffold in drug design and therapeutic leads. Various *s*-triazine analogs have been synthesized and tested for a variety of pharmacological actions. Some compounds display significant pharmacological profile and may serve as a key target in the creation of new therapeutic arenas. Though number of compounds that have advanced into human clinical trials is small, yet the promise of discovering safe molecules, effective in remediation particularly for cancer still needs more effort. The pharmacological characteristics of *s*-triazine analogs shall be presented in current review.

Keywords: *s-Triazine, pan PI3K inhibitors, isoform-selective PI3K inhibitors, mTOR inhibitors.*

I. Introduction

Three nitrogen atoms replace the carbon-hydrogen units in the benzene ring structure in triazines that forms a fascinating class of aromatic heterocyclic molecules with the chemical formula $C_3H_3N_3$. Based on the position of the nitrogen atom, there are three different triazine systems: 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine have been categorized (Fig.1). 1,3,5-triazine is also known as *s*-triazine or symmetrical triazine. *s*-Triazine is the oldest and best studied of the isomeric forms.[1-6] Many of the lead molecules having pharmacologist properties currently in different phases of clinical trials have s-triazine as their core moiety. Hence it warrants having special attention.

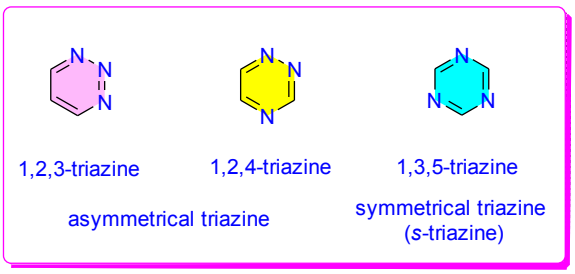

Fig. 1: Triazine isomers

s-Triazine moieties are an intriguing class of compounds having a variety of physiological effects including anti-cancer, antiviral, fungicidal, insecticidal, bactericidal, herbicidal, antimicrobial, and anti malarial effects (Fig.2)[3, 5, 7, 8], and become crucial building blocks for the creation of novel therapeutic medicines.

Furthermore, numerous *s*-triazine derivatives have demonstrated to show promising properties for further research as brand-new anticancer drugs. [7, 9, 10]. *s*-Triazine compounds with antitumor activity have received a lot of interest. *s*-Triazine derivative known as hexamethylmelamine[HMM] or altretamine has been approved by FDA for the treatment of refractory ovarian cancer.[11, 12] The regulatory activity of HMM

is due to HMPMM [hydroxymethylpentamethylmelamine] moiety. Hydroxymethylpentamethylmelamine [HMPMM] was synthesised and evaluated for anticancer

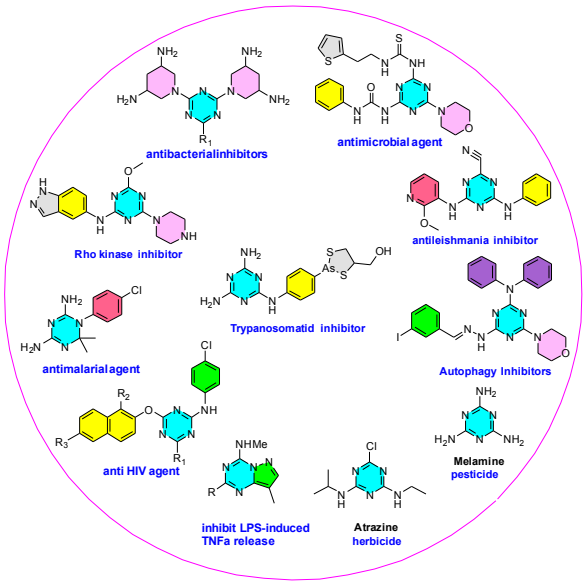

Fig 2: *s*-Triazine containing bioactive molecules against various targets.

potential (Fig. 3).

The most intriguing chemical core structures explored is the *s*-triazine skeleton and its derivatives having a wide variety of bioactivity uses. The primary objective of this literature analysis is to address the formaton of *s*-triazine based compounds as a different inhibitors like PI3K, mTOR, dual PI3K/mTOR, dual MEK/PI3K, CDK, RTK (Fig. 3). *s*-Triazine derivatives hexamethyl melamine (altretamine), Triethylenemelamine (Tretamine) are FDA approved anticancer drugs. Gedatolisib

(PI3K/mTOR inhibitor) and HL010183 (inhibits triple negative breast cancer cells) are other commercially approved drugs bearing *s*-triazine moiety. It is now more commonly known that PI3K drugs mostly show antiproliferative activity rather than cytotoxicity. The development of PI3K pathway antagonists has been impeded by poor drug tolerance, innate and acquired resistance to antibiotics, and also signaling feedback loops that reverse PI3K inhibition. The PI3K inhibition requires tri-substituted *s*-triazine as key pharmacophoric structure with potent activity and better physico-chemical and pharmacokinetic properties.

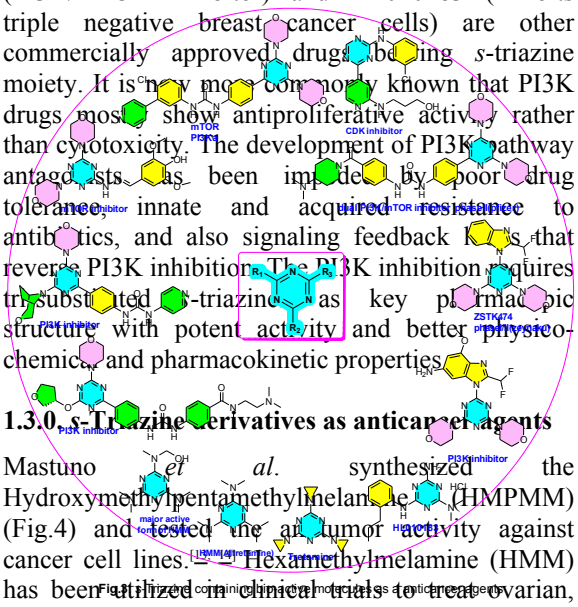

Fig. 3: Triazine containing clinical molecules as anticancer agents

1.3.0 *s*-Triazine derivatives as anticancer agents

Mastuno *et al.* synthesized the Hydroxymethylpentamethylmelanine (HMPMM) (Fig.4) and tested the antitumor activity against cancer cell lines.[7, 9, 10, 13, 14] Hexamethylmelamine (HMM) has been utilized in clinical trials to treat ovarian, lung and breast cancer.

The same research groups synthesized the compound **3** (Fig. 4) showing significant aromatase inhibitory activity. Compound **3** shows better antitumor activity than compound (**2**) in human cancer cell lines (Fig.4). When imidazolyl group (**3**) was replaced with benzimidzole group (**4**), it showed enhanced potency in human cancer cell lines (Fig. 4).[7, 9, 10, 13, 14]

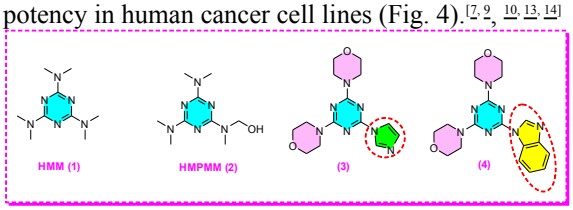

Fig. 4: 1,3,5-triazine scaffold as clinical candidate

To address the issue of poor aqueous solubility of ZSTK474 Rewcastle *et al.* started a medicinal chemistry programme on ZSTK474 scaffold to rationally modify it for better aqueous solubility with retention of pharmacological profile. Among synthesized analogs, compound **6** shows very potent activity in nanomolar scale against PI3K and better aqueous solubility (Fig.**5**).The benzimidazole cycle of ZSTK474 can tolerate changes at positions 4 and 6 however a substitution at position 5 reduces its activity. Compound **6** was the most potent having IC_{50} value in nanomolar range as shown in figure 5.

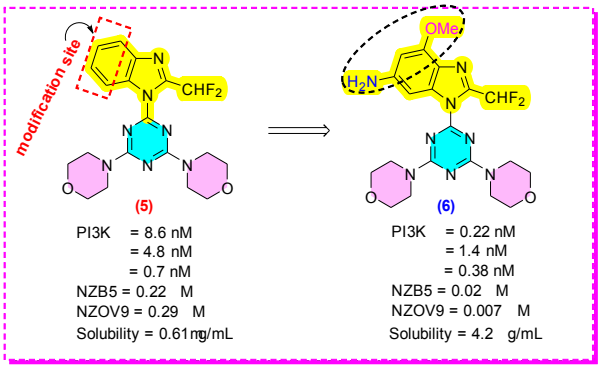

Fig. 5: Substituted benzimidazole derivatives

Narva *et al.*[16] synthesised a series of *s*-triazine analogues, which were then described and tested for cytotoxicity assay. *s*-Triazine analogues showed potential anti-proliferative efficacy against various cancer cell lines. Compound **7 (**Fig. 6**)** was found to have significant action against HeLa, HepG2, A549, and MCF-7, with IC_{50} values of 12.3, 9.6, 10.5, and 11.7 *u*M respectively. Compound **7** inhibits tubulin polymerization. Compound **7** has a strong binding interaction of -7.949 towards the nocodazole binding site of tubulin.

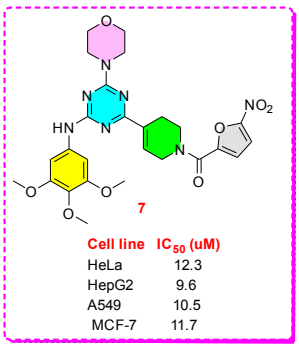

Fig. 6: *s*-Triazine based antiproliferative agent

Wyeth Research Co. also produced *s*-triazine based PI3K inhibitors with two morpholine rings. To improve polarity and water solubility, *s*-triazine was chosen as the core scaffold. But this ring is frequently metabolically oxidized, so a second morpholine group was added to it. Out of all the synthesized analogs, compound **8** showed a high potency against various cancer cell lines and thus selected for additional *in vitro* and *in vivo* investigation. A number of human tumour xenografts, including MDA-361, U87MG, and colon HCT116, were used in preclinical studies to demonstrate the compound **8**'s antitumor efficacy (Fig. 7). These studies also demonstrated that the compound **8** had a favorable pharmacokinetic profile. Phase II of clinical trials for Compound **8** have been completed.

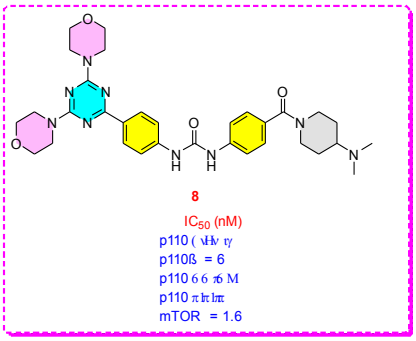

Fig. 7: *s*-triazine scaffold as clinical candidate

1.3.1.1. Pan PI3K inhibitors

Norman *et al.*[17] reported that Pyridyltriazine **9** (Fig. 8) was a strong pan PI3K-inhibitor with an excellent pharmacokinetic profile. In a mouse liver pharmacodynamic model, compound **9** was demonstrated to effectively block the targeted PI3K pathway with an EC_{50} of 228 ng/mL. This led to the selection of the compound **9** for further evaluation as a potential clinical candidate.

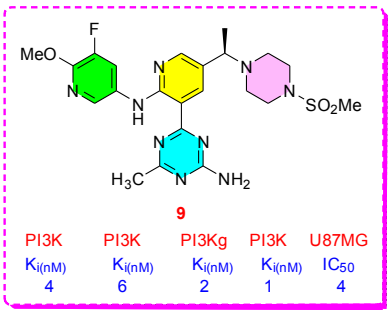

Fig. 8: Pan PI3K inhibitor

1.3.1.2. Selective inhibitor of class I PI3Ks

According to the recent clinical data isospecific PI3K inhibitors have high rate of success in drug design in comparison to pan PI3K inhibitors. Smith *et al.* developed many pyridine substituted triazine derivatives in 2012, with compound **10** (Figure 9) displaying the highest activity and PI3K selectivity over mTOR. When administered orally at doses of 25 and 75 mg/kg for 8 hours, compound **10** effectively reduced the HGF-induced phosphorylation of Akt. When administered at a higher dose in the liver, compound **10** maintained this inhibition for 24 hours.

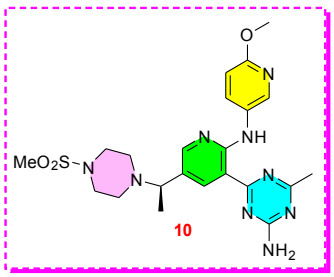

Fig. 9: PI3Kα selective inhibitor

Pinson *et al.* have designated some effective and isoform-selective PI3K inhibitors using aminoacyl triazines on the basis of ZSTK474. Comparing these inhibitors to other selective inhibitors, they demonstrate a different molecular foundation for selectivity. Compound **11** containing L-Phe (Figure 10) was 35-fold more selective for PI3K than PI3K. When it came to promoting cell growth, compound **11** was just as effective as ZSTK474 and had IC_{50} values that were less than 10 nM for cellular Akt phosphorylation.

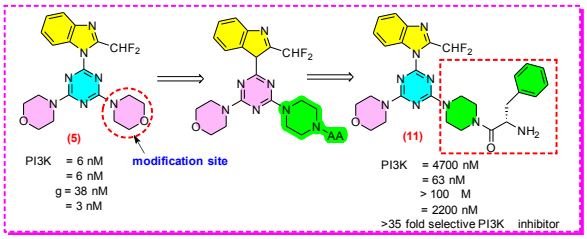

Fig. 10: PI3Kβ selective inhibitors

1.3.2. *s*-Triazine derivatives as mTOR inhibitors

Verheijen *et al.*[18] synthesized a series of compounds and tested their mTOR activity, compound **12** was shown the better activity (Fig.11).The absence of reduction of AKT phosphorylation, a PI3K/PDK1 biomarker, provided evidence of the selective nature of inhibitor **12**. Compound **13** showed the most promising combination of potency, selectivity, and acceptable pharmacokinetic features. Peterson *et al.*[19] synthesized and evaluated the *in vivo* mTOR activity of a series of *s*-triazine based analogs. Among all synthesized analogs, inhibitor **13** was injected intraperitoneally (IP) into mice at doses of 10, 30, and 100 mg/kg (N=3 animals/group), and it showed remarkable selectivity for mTOR (Fig. 13). At a dosage of 100 mg/kg, the mean unbound plasma concentration was 0.65 uM, which was more than six times the cellular IC_{50} for AKT and 1.6 times the cellular IC_{50} for pS6. Zask *et al.* produced a series of 3,5-ethylene bridged morpholine-containing compounds and out of that, analog **14** was obtained with a 10-fold increase in selectivity against PI3K isoforms (Fig 11). The mTOR biomarker S473 was selectively inhibited in comparison to the PI3K T308 biomarker due to the mTOR selectivity of **14**. Upon administering nude mice with MDA361 tumours with 10 or 25 mpk of **16**, it was likewise seen that

after 8 hours, the S473 biomarker was suppressed *in vivo* more so than the T308 biomarker. In the U87MG nude mice xenograft experiment, **14** demonstrated significant tumour growth suppression with daily oral dose of X5. Among all compounds, 3-pyridyl urea, bis-(*R*)-3-methylmorpholine **15**(Fig.11) shown the better mTOR activity. As a result, compounds with alkyl ureas on the triazine scaffold had much lower potencies than those with aryl urea. Zhu *et al.* synthesized a series of compounds, among all **16** was shown to have better mTOR activity (Fig.11).The activity was improved by a smaller atom or group within the ring, and the substituents on the benzene ring also significantly influenced the antiproliferative action.

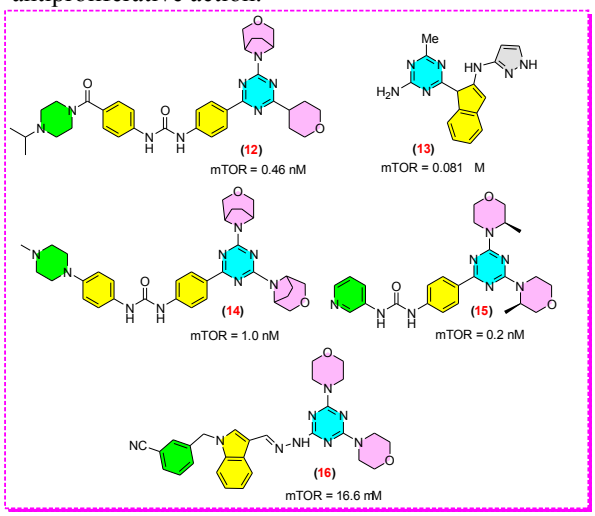

Fig. 11: mTOR inhibitors

Menear *et al.*[20]used a pharmacophore mapping approach to discover a number of selective mTOR inhibitors. A hit discovered through pharmacophore analysis led to the discovery of a novel tri-substituted *s*-triazine scaffold with effective and selective inhibitors activity for mTOR (Fig 12). The compounds were thoroughly optimized, and a variety of highly effective and targeted inhibitors of the mTOR kinase enzyme were found.

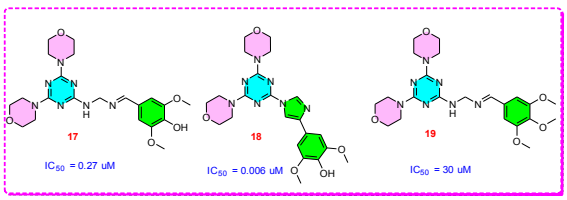

Fig. 12: mTOR inhibitors

Zask *et al.*[21] reported that when bridged morpholines were incorporated into monocyclic *s*-triazine scaffold results in PI3K/mTOR inhibitor activity **20** (Fig. 13) with higher mTOR selectivity than the morpholine analogs. mTOR inhibitors with ureidophenyl groups were shown to be highly powerful and selective. Biomarker suppression experiments were used to demonstrate potency and selectivity *in vitro* and *in vivo*. Upon PO and IV dosing, several drugs showed effective suppression of tumor growth in nude mouse xenograft experiments.

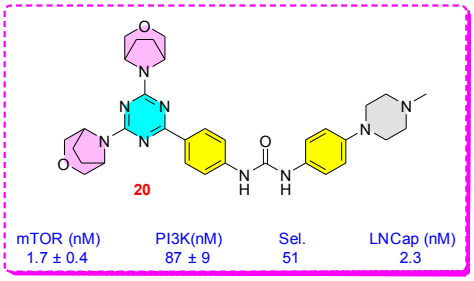

Fig. 13: mTOR inhibitors

Peterson *et al.*[19] discovered *s*-triazine benzimidazole inhibitors, which have been demonstrated to show 200-fold selectivity for mTOR over the structurally homologous enzyme PI3K and modest selectivity for the PIKK family of kinases by combining a specific SAR and data from PI3K co-crystal structures obtained using X-rays. Compound **21** (Fig. 14) exhibited the potent mTOR potency and selectivity over other kinases. Pharmacokinetic properties were explored *in vivo* in mouse model study despite its relatively high *in vivo* clearance and low solubility. pAKT, a downstream substrate of mTOR kinase, was suppressed by inhibitor **21** up to 83 percent in a dose-dependent manner.

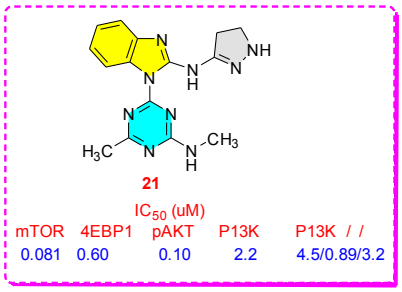

Fig. 14: mTOR inhibitors

1.3.3. *s*-Triazine derivatives as dual PI3K/mTOR inhibitors

Wurz *et al.* recently synthesized compounds **22** and **23**, a novel dual PI3K/mTOR inhibitor that has a 4-amino-6-methyl-s-triazine sulfonamide scaffold (Fig 15). Compound **24** (Fig. 15) demonstrated greater solubility and an enhanced PK profile in comparison to compound (**22**). In addition to this compound 22 show highly selective against 50 other kinases in comparison to compound (**23**). Compound (**24**), with an EC_{50} value of 193 nM (91 ng/mL), was effective in a tumour PD experiment in mice.

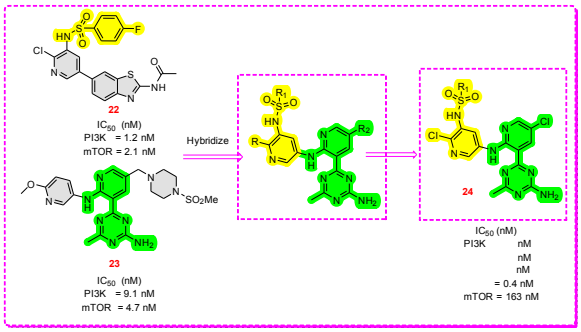

Fig. 15: Development of dual PI3K/mTOR inhibitor

Unsymmetrical diarylureas has been synthesised as strong inhibitors of both PI3K and mTOR signaling (Fig 16). Many studies have shown that PI3K/mTOR inhibitors have synergistic effects; using both signaling medications together can prevent drug resistance and tumour migration in breast cancer. As a result, developing compounds that inhibit both of these routes at the same time is critical. Mechanistic studies revealed that the representative drug (**25**) inhibits both PI3K/mTOR signaling and apoptosis in T47D and MDA-MB-231 cells.

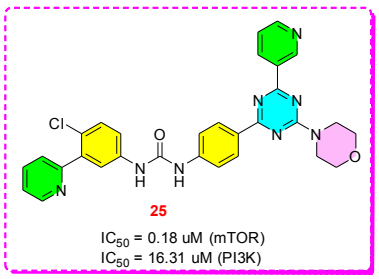

Fig. 16: Dual PI3K/mTOR inhibitor

1.3.4. *s*-Triazine as mitogen-activated protein kinase (MEK) and PI3K inhibitors

More activity against MEK or PI3K inhibitor monotherapy is anticipated with dual targeted kinase inhibitors. A single MEK/PI3K dual inhibitor may also be safer and more beneficial than a fusion of two therapeutic drugs that each target a different pathway. Dort *et al*. synthesized compound **27**(Fig. 17) which exhibits dual MEK/PI3K inhibitory activity. This is an illustration of an allosteric MEK inhibitor covalently coupled to a PI3K inhibitor that keeps a reasonably high affinity for both targets.

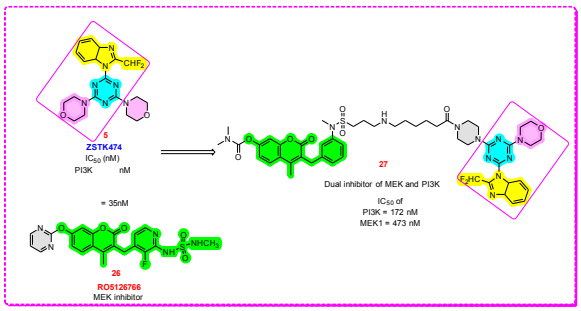

Fig. 17: Dual MEK/PI3K inhibitor

1.3.5. *s*-Triazine derivatives as CDK inhibitors

Cyclin-dependent kinases (CDKs) play a crucial role in controlling the cell cycle apparatus. These family kinases can only be activated by the cycling mediator subunit, and different CDK/cyclin pairs control the cell cycle at different stages. Over the past ten years, various CDK inhibitors have been studied. With an IC_{50} of 0.021 uM, CDK1, CDK2, and CDK5 were all competitively suppressed by the novel, strong *s*-triazine-based CDK inhibitor **28** (Figure 18), while CDK4, CDK6, and CDK7 shown submissive efficacy and considerable GSK-3 potential. It effectively slowed down the growth of several tumour cell lines, including A375, U937, HCT-116, and HeLa. In human A375 xenograft models, compound **28** increased the effective survival of nude mice when given intraperitoneally at doses of 150 and 125 mg/kg. Compound **28** makes extensive favorable vander Waals interactions with the binding site through its main scaffold and fits well into the ATP binding site of CDK.[22]

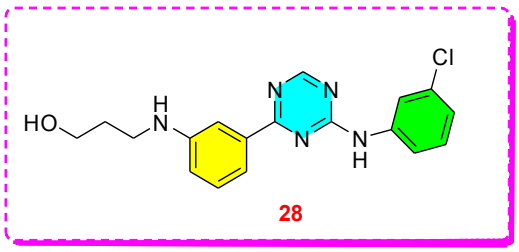

Fig. 18: *s*-Triazine scaffold based CDK inhibitor

II. Conclusions

The findings emphasize the importance of the *s*-triazine scaffold in medicinal chemistry as a result of its diverse range of biological features including anticancer activity. Many instances stood out among this class of drugs for their powerful anticancer efficacy and particular target selectivity, and some of them progressed to clinical development.

References

[1]. Jain, S., et al., Use of 2,4,6-trichloro-1,3,5-triazine (TCT) as organic catalyst in organic synthesis. Synthetic Communications, 2016. **46**(14): p. 1155-1174.

[2]. Blotny, G., Recent Applications of 2,4,6-Trichloro-1,3,5-triazine and Its Derivatives in Organic Synthesis. Cheminform, 2006. **37**.

[3]. Deepak Kumar Basedia, B.K.D., Birendra Shrivastava A Review on Synthesis and Biological activity of Heterocyclic Compounds bearing 1, 3, 5-Triazine Lead Moiety. American Journal of PharmTech Research 2011. **1**(4): p.: 174-193.

[4]. HATFIELD, S.E., APPLICATIONS OF TRIAZINE CHEMISTRY: EDUCATION, REMEDIATION, AND DRUG DELIVERY 2007, Texas A&M University: Texas A&M University.
[5]. Rajeev Kumar1, N.K., Ram Kumar Roy, and Anita Singh, Triazines – A comprehensive review of their synthesis and diverse biological importance. Curr Med Drug Res, 2017.
[6]. Sharma, A., et al., s-Triazine: A Privileged Structure for Drug Discovery and Bioconjugation. Molecules, 2021. **26**(4): p. 864.
[7]. Cascioferro, S., et al., 1,3,5-Triazines: A promising scaffold for anticancer drugs development. European Journal of Medicinal Chemistry, 2017. **142**: p. 523-549.
[8]. el-samahy, F., et al., Synthesis and antimicrobial activity of new substituted 1,3,5-triazine derivatives. 2016. **9**: p. 436-445.
[9]. Calvete, M.J.F., et al., Multifunctionalization of cyanuric chloride for the stepwise synthesis of potential multimodal imaging chemical entities. Arabian Journal of Chemistry, 2020. **13**(1): p. 2517-2525.
[10]. Kothayer, H., et al., Design, synthesis and in vitro anticancer evaluation of 4,6-diamino-1,3,5-triazine-2-carbohydrazides and -carboxamides. Bioorganic & Medicinal Chemistry Letters, 2013. **23**(24): p. 6886-6889.
[11]. Hedayatullah, M.L., C.; Slimane, A. B.; Da Conceição, L.; Nachawati, I, Heterocycles, 1999. **51**(51): p. 1891-1896.
[12]. Garaj, V.P., L.; Fasolis, G.; Winum, J.-Y.; Montero, J.-L.; Scozzafava, A.; Vullo, D.; Innocenti, A.; Supuran, C. T, Bioorg. Med. Chem. Lett. , 2005. **15**(15): p. 3102.
[13]. Matsuno, T.K., M.; Sasahara, H.; Watanabe, T.; Inaba, M.; Takahashi, M.; Yaguchi, S.-I., and K.S. Yoshioka, M.; Kawashima, S, Chem. Pharm. Bull. . Chem. Pharm. Bull, 2000. **48, 1778**: p. 1778.
[14]. Matsuno, T.K., M.; Tsuchida, Y.; Takahashi, M.; Yaguchi, S.; Terada, S., Chem. Pharm. Bull. , 1997, . **45,** : p. 291.
[15]. Janku, F., T.A. Yap, and F. Meric-Bernstam, Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol, 2018. **15**(5): p. 273-291.
[16]. Narva, S., et al., Design and synthesis of 4-morpholino-6-(1,2,3,6-tetrahydropyridin-4-yl)-N-(3,4,5-trimethoxyphenyl)-1,3,5-triazin-2-amine analogues as tubulin polymerization inhibitors. Bioorganic & Medicinal Chemistry Letters, 2017. **27**(16): p. 3794-3801.
[17]. Norman, M.H., et al., Selective Class I Phosphoinositide 3-Kinase Inhibitors: Optimization of a Series of Pyridyltriazines Leading to the Identification of a Clinical Candidate, AMG 511. Journal of Medicinal Chemistry, 2012. **55**(17): p. 7796-7816.
[18]. Ciuffreda, L., et al., The mTOR pathway: a new target in cancer therapy. Current cancer drug targets, 2010. **10**(5): p. 484-495.
[19]. Peterson, E.A., et al., Discovery of triazine-benzimidazoles as selective inhibitors of mTOR. Bioorganic & Medicinal Chemistry Letters, 2011. **21**(7): p. 2064-2070.
[20]. Menear, K.A., et al., Identification and optimisation of novel and selective small molecular weight kinase inhibitors of mTOR. Bioorganic & Medicinal Chemistry Letters, 2009. **19**(20): p. 5898-5901.
[21]. Zask, A., et al., Discovery of 2-ureidophenyltriazines bearing bridged morpholines as potent and selective ATP-competitive mTOR inhibitors. Bioorg Med Chem Lett, 2010. **20**(8): p. 2644-7.
[22]. Kuo, G.H., et al., Synthesis and identification of [1,3,5]triazine-pyridine biheteroaryl as a novel series of potent cyclin-dependent kinase inhibitors. J Med Chem, 2005. **48**(14): p. 4535-46.
[23]. Baindur, N., et al., 2-Hydroxy-4,6-diamino-[1,3,5]triazines: A Novel Class of VEGF-R2 (KDR) Tyrosine Kinase Inhibitors. Journal of Medicinal Chemistry, 2005. **48**(6): p. 1717-1720.
[24]. Katiyar, S.B.S., K.; Puri, S. K.; Chauhan, P. M. S, Bioorg. Med. Chem. Lett. , 2005. **15**: p. 4957.
[25]. Chauhan, K.S., M.; Shivahare, R.; Debnath, U.; Suman Gupta; Prabhakar, Y. S.; Chauhan, a. P. M. S., ACS Med. Chem. Lett. , 2013,. **4,**: p. 1108.