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REVIEW ARTICLE

Novel pyridine and pyrimidine derivatives as promising anticancer agents: A review

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Abstract Pyridines and pyrimidines are the class of heterocyclic nitrogenous compounds having plethora of applications in anticancer drug development. These synthetic sources serve as the potent class of compounds in treatment of breast cancer, myeloid leukemia, pancreatic cancer, liver cancer and idiopathic respiratory fibrosis etc. The present review enumerates the results of studies published during past three years (2019–2021) on pyridine and pyrimidine analogues with their respective anticancer properties characterized *in vitro* or through *in silico* studies and illustrates their potential in development of anticancer agents. Recent advances on pyridine and pyrimidine analogues mentioned in this review add to the appealing opportunities for cancer therapy.

Contents

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1. Introduction

Cancer is a universal health concern which affects a huge human population. Attributed to the world's primary cause of fatality, approximately 19.3 million recent cases and nearly 10 million deaths took place because of some sort of cancer in the year 2020 (Sung et al., 2021). Out of these, lung cancer topped the list with projected 18% (1.8 million) deaths and subsequent 9.4%, 8.3%, 7.7% and 6.9% deaths were due to colorectal, liver, stomach, and female breast cancers, respectively. A global rise of 47% in new cancer cases are anticipated in 2040 with respect to the year 2020 (Sung et al., 2021) highlighting the need for new therapeutic agents to combat the disease.

Heteroatoms including heterocyclic blocks provide an appealing opportunity to identify new molecules for cancer treatment. Scientifically, over 85% of all compounds exhibiting biological activity are heterocycles, or consist of a heterocycle, and most often, nitrogen heterocycles being a backbone in their intricate structures. These particulars reveal and draw attention to the crucial role of heterocycles in progressive drug design and discovery (Heravi and Zadsirjan 2020). Among these, nitrogen containing heterocyclic compounds is most prevalent in the form of hormones, vitamins, and antibiotics (Heravi and Zadsirjan 2020). As per the FDA databases, 60% of the exclusive drugs (small molecule) consist of N-containing heterocycles, exhibiting the structural importance of these nitrogen containing heterocyclic compounds in drug designing and discovery (Martins et al., 2015; Ajani et al., 2017). The incidence of nitrogen heterocylces in biologically active compounds can be ascribed to their functional proficiency and stability in human anatomy and the evidence that the N- atoms are readily bonded to DNA *via* hydrogen bonding. The anti-tumor activities of nitrogen based heterocyclic agents are fundamentally attributed to their affinity to DNA through hydrogen bonding (Ozkay et al., 2010). The majority of FDA accepted drugs exhibit a pyrimidine or pyridine nucleus bearing diverse substituents (Chiacchio et al., 2019). Moreover, pyridine and pyrimidine derivatives serve as promising anticancer agents in the field of cancer research. Natural products and genetic materials contain pyridine and pyrimidine. These pyridine/pyrimidine backbone structures (Fig. 1) have been linked to a variety of biological processes, including cancer pathogenesis. Pyridine and pyrimidine derivatives have acquired huge attention in current medicinal research due to their impact in curing of numerous vicious ailments, like breast cancer, myeloid leukemia, and idiopathic respiratory fibrosis (Chiacchio et al., 2019; Prachayasittikul et al., 2017). Some of the approved drugs with pyridine pharmacophores are Sorafenib **I** (Fig. 2**a**), Regorafenib **II** (Fig. 2**b**), Vismodegib **III** (Fig. 2**c**) and Crizotinib **IV** (Fig. 2**d**) while the marketed drugs having pyrimidine moiety are Gemcitabine (Fig. 2**e**), 5-Fluorouracil (Fig. 2**f**) and Floxuridine (Fig. 2**g**).

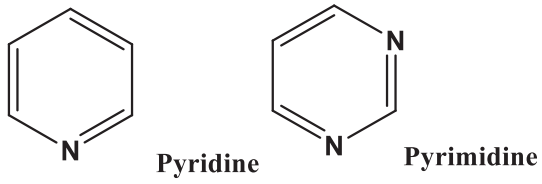

Fig. 1 Basic ring structures of pyridine and pyrimidine.

Formation of the pyridine ring system and the derivatives inhabit a significant space in the world of synthetic organic chemistry, owing to their medicinal and pharmaceutical properties (Srivastava et al., 2007). They have become apparent as fundamental backbones of more than 7000 accessible drugs. On the other hand, pyrimidine derivatives are deemed vital for drugs and agriculture related chemicals. Pyrimidines are significantly involved in successful curing many of the diseases. Pyrimidine derivatives acquire quite a lot of remarkable biological activities for example anti-tumor, antimicrobial, and antifungal activities in addition to its use in thyroid and leukaemia drugs (Patel et al., 2012).

The present review enumerates the results of different studies on pyridine and pyrimidine nuclei with anticancer properties and describes their potential in development of anticancer agents.

2. Pyridine derivatives as anticancer agents (2019–2021)

Numerous synthetic drugs are good chemotherapeutic agents. Pyridines constitute the class of nitrogenous heterocycles which undergo different chemical synthesis routes for generation of novel compounds demonstrating anticancer/antitumor properties. There are many synthetic derivatives prepared for the pyridines, however, in this review we will discuss the novel ones past 3 years i.e. between the years 2019–2021 which have been characterized *in vitro* or through *in silico* studies. A consolidated list is included in Table 1.

2.1. Classification of pyridine derivatives based on the biological action

2.1.1. Synthetic pyridine derivatives involved in cell cycle regulation

Bathula et al. (2019) reported newly designed Pyrido[2,1-b] quinazoline fused derivatives having good medicinal properties. These designed compounds were tested for cytotoxic actions *via* the *in vitro* studies countering to an array of malignant cell lines including NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145. Compound **1 i.e.** 1-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline (**Fig. S1**) exhibited the highest cytotoxic action over the lung cancer cell lines, A549 and NCI-H460. In addition, the same compound was demonstrated to have a potent anticlonogenic impact on lung cancer cells. Under flow cytometry this unique compound was observed to block the G_0/G_1 cell cycle phase in the A549 malignant cell lines. Molecular dock-

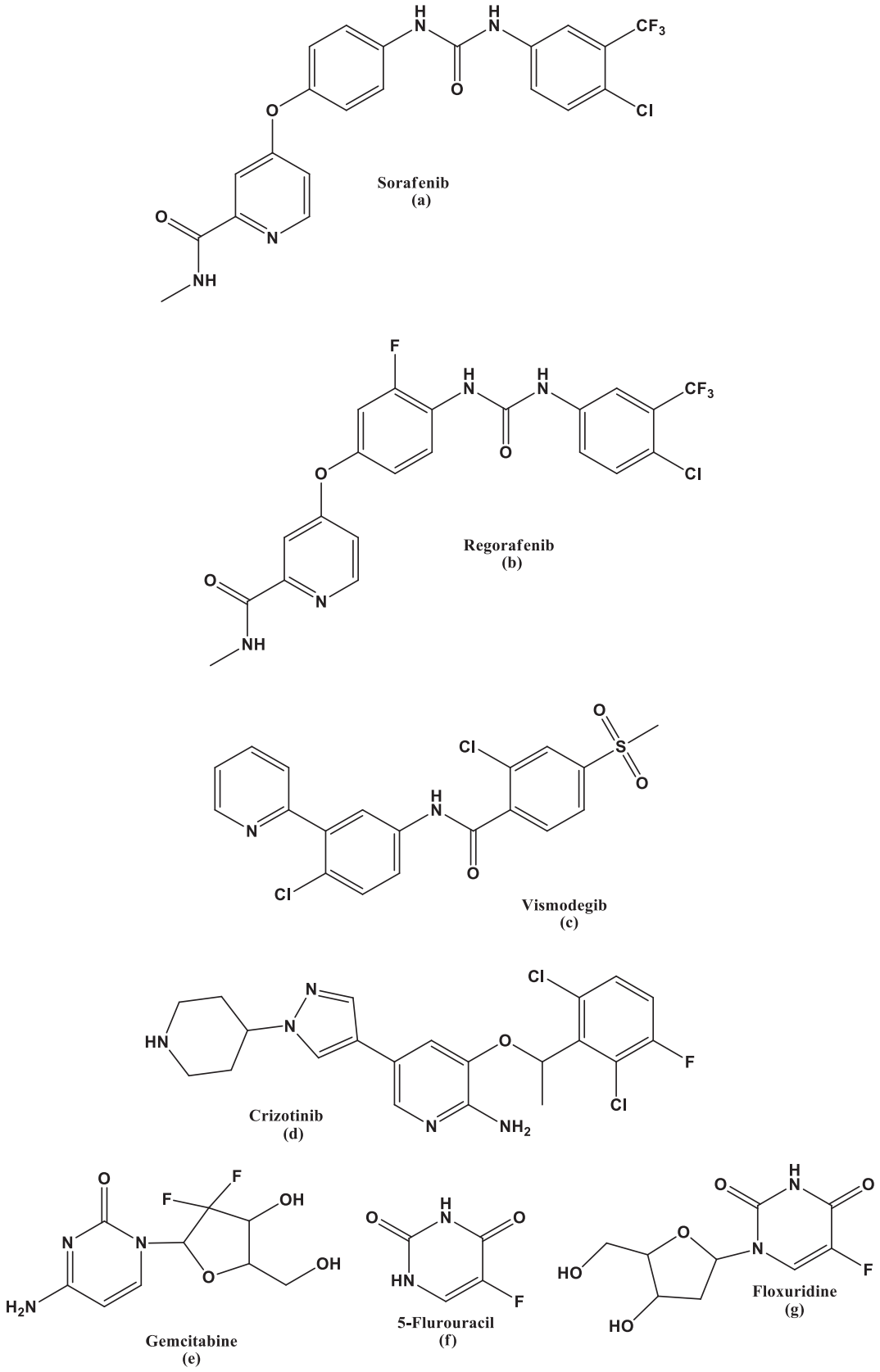

Fig. 2 Marketed anticancer drugs with pyridine **(a-d)** and pyrimidine **(e-f)** moieties.

Table 1 Synthetic pyridine derivatives with anticancer activity.

Year	Author	Compound	*In vitro studies*	*In silico studies/ Possible targets*	Cell lines
Cell cycle regulatory activity					
2019	Bathula et al.	11-(1-Benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline	Cytotoxic, anti-clonogenic; G_0/G_1 cell cycle phase inhibitor	EGFR kinase	NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145
2019	Fayed et al.	Coumarin-pyridine/fused pyridine hybrids	Growth inhibitors at G_2/M phase, apoptotic cell death		HCT-116, MCF-7, A549, and HepG-2
2019	Xu et al.	Pyridine-chalcone analogues	G_2/M phase inhibition; anticancer	Anti-tubulin compounds	H22 xenograft models
2020	Jian et al	Pyrazolo[3,4-b]pyridine-bridged derivatives of combretastatin A-4 acquiring 3,4,5-trimethoxylphenyl groups	Anti-proliferative actions, G_2/M stage arrest	Tubulin polymerization inhibition	HeLa
2021	Zwergel et al.	Aza-analogues like the regioisomers from the N-hydroxy-3-(4-(2-phenylbutanoyl)amino)phenyl) acrylamide comprising pyridine nucleus	G_2/M stage inhibition	HDACs	U937, K562, HCT116, A549
Anti-tumorigenic activity					
2019	Hassan et al.	Thieno[2,3-b]pyridine analogues	Anti-tumor activity		HepG-2 and MCF-7 cell
2019	Murugavel et al.	Heterocyclic sulfur thiophene analogue including pyridine and 1,2,3-triazole components	Anti-proliferative	Human topoisomerase IIα targeting ATP binding site	PC-3, A549 and MDAMB-231
2019	Zeidan et al.	Picolinamide derivatives acquiring dithiocarbamate and (thio)urea moieties	Anti-tumor action	VEGFR-2 kinase inhibitors	A549, OVCAR-3, Panc-1, HT29, 786-O
2021	Hassan et al.	Pyridine and fused pyridine derivatives	Anti-tumor action		HepG2, MCF-7
Cytotoxic activity					
2020	Behbehani et al.	Substituted 6,7-dihydro-5H-benzo[6,7]cyclohepta [1,2-b]pyridine and 5,6-dihydrobenzo[h]quinoline systems	Cytotoxicity		A549, MCF-7, HCT-116
2020	Suma et al.	Chalcone linked thiazole-imidazopyridine analogues library	Cytotoxicity		MCF-7, A549, DU-145, MDA MB-231
2021	Keshk and Izzularab	Cyanopyridines, pyridopyrazolotriazines and pyridopyrazolopyrimidines	Cytotoxicity		HepG-2, PANC-1, A-549

ing studies of the compounds **2a** and **2b** with erlotinib as control for predicting the binding to the EGFR kinase were also performed. The compounds under investigation showed the analogous interactions in comparison to erlotinib. The study concluded that the compound 11-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline could serve as a lead anticancer agent.

New series of 16 coumarin-pyridine/fused pyridine hybrids was created by Fayed and coworkers (Fayed et al., 2019) and tested for the anticancer property over human cancer cell lines HCT-116, MCF-7, A549, and HepG-2. Out of the 16 compounds in total, compound **1, 2** and **3** (**Fig. S2**) were found to be most potent growth inhibitors against cell line MCF-7 detaining the cell cycle in the G_2/M phase and subsequently apoptotic cell death. In coherence with these results, caspase-3 activity in MCF-7 cells was also evaluated. The results designated the significant augmentation of caspase-3 activity by compounds **1, 2,** and **3** in comparison to the control group. Additionally, binding affinity of all the three compounds for caspase-3 was established by docking analysis using MOE software (MOE 2008.10). Altogether, it was deciphered that these coumarin derivatives might prove to be promising anti-proliferative agents.

While improving the trimethoxyphenyl backbone of master chalcone complex by bringing in a pyridine ring, Xu et al. (2019) presented an array of 19 new pyridine-chalcone analogues as potent anti-tubulin compounds. Every single compound under investigation was assayed for their anti-proliferative actions. Amid them, compound **1** (**Fig. S3**) was found having the highest potential over a group of malignant cell lines. Subsequent studies verified inhibitory role of compound **1** in polymerization of microtubule by associating to the colchicine position of tubulin. Besides, it was revealed that compound **1** leads to G_2/M phase inhibition. Notably, compound 1 prominently impeded cancer development in H22 xenograft models with no evident noxious effect, stringent than the control compound CA-4, signifying that it is worthy investigating compound **1** as a potential microtubule-destabilizing agent in treatment of malignancy.

Jian et al. (2020) reported synthesis of 26 new pyrazolo[3,4-*b*]pyridine-bridged derivatives of combretastatin A-4 acquiring 3,4,5-trimethoxylphenyl groups, and assessed their tubulin

polymerization inhibitory and anti-proliferative actions. Initial biological assessment established that few of the candidate compounds showed considerable anti-proliferative action countering four varying cell lines comprising MDA-MB-231, MCF-7, Kyse150 and HeLa. Compound **1** (**Fig. S4**) proved to be the highly potent pyridine derivative as it induced HeLa cells arrest in the G_2/M stage *via* dose dependent manner. Molecular modeling investigation suggested that analogue **1** apparently dwells in the colchicine spot of tubulin. The preliminary outcomes are indicative in proving 3,4,5-trimethoxyphenyl substituted pyrazolo[3,4-*b*]pyridine to be a competent scaffold intended in developing effective tubulin barrier as antineoplastic agents.

Zwergel et al. (2021) synthesized four aza-analogues like the regioisomers from the N-hydroxy-3-(4-(2-phenylbutanoyl)amino)phenyl)acrylamide comprising pyridine nucleus as prior reported by the same group as a HDAC inhibitor. Initial screening countering to mHDAC1 indicated N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide as the highly effective inhibitor. Consequently, both pyridylacrylic- and nicotinic-based hydroxamates (11 compounds) and 2′-aminoanilides (12 compounds), linked to N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide were developed by the team of same researchers which required testing against HDACs. Amid all, one nicotinic hydroxamate demonstrated sub-nanomolar potency and selectivity up to 34,000 times compared to HDAC4 and 100 to 1300 times with respect to the entirely evaluated HDAC isoforms. Three other hydroxamates **1, 2** and **3** inhibited more than 80% of cells in G_2/M stage of cell cycle upon evaluation in U937 leukemia cells; on the other hand, the anilides brought no change in the cell-cycle progress. While the one each of hydroxamate **2** and the anilide **1** accelerated around 30% apoptosis, and the anilide **2** exhibited ~ 40% cytodifferentiation in the same cell line. Ultimately, the highly effective analogues in leukemia cells N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide**,** hydroxamate **2,** anilide **1, 2** and **3** (**Fig. S5**) were also assayed against K562, HCT116, and A549 cancer cells, exhibiting anti-proliferative activity.

2.1.2. Synthetic pyridine derivatives acquiring anti-tumorigenic properties

On the basis of the established anticancer properties of thieno [2,3-b] pyridines Hassan et al. (2019) planned to synthesize new thieno[2,3-b]pyridine analogues assimilating diverse biologically active heterocycles *via* several chemical reactions. Total 44 compounds were synthesized, and these newly synthesized derivatives were assayed for anti-tumor activity over HepG-2 and MCF-7 cell lines with respect to doxorubicin (standard anticancer drug). Outcomes of the study suggested that out of the total 44 compounds, compound **1, 2, 3** and **4** (**Fig. S6**) acquired highest potency over both the cell lines and compound **2** was found to be more potent than doxorubicin standard against HepG-2 cell line.

Murugavel et al. (2019) presented in their work, the computational quantum compound investigation in addition to the biological assessment of a newly synthesized heterocyclic sulfur thiophene analogue including pyridine and 1,2,3-triazole components *viz*. BTPT [2-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-6-methoxy-4-(thiophen-2-yl) pyridine] (**Fig. S7**). Drug resemblance factors of BTPT were searched *via in silico* medicinal ADMET attributes evaluation. Human topoisomerase IIα targeting ATP binding site was used to perform molecular docking studies. MTT assay was conducted over the three human malignant cell lines PC-3, A549 and MDAMB-231 for the *in vitro* cytotoxicity test of BTPT/doxorubicin. The lead compound BTPT showed considerable cytotoxicity against MDAMB-231 (breast cancer cell), mild activity with A-549 (human lung cancer cell) and least inhibition with PC-3 (human prostate cancer cell) in comparison to the known cancer drug doxorubicin. It was inferred that BTPT could serve as a potent candidate for anticancer drug.

Zeidan et al. (2019) planned and produced two series of picolinamide derivatives acquiring dithiocarbamate and (thio)urea moieties as VEGFR-2 kinase inhibitors. Cytotoxicity of all the new 9 compounds was screened hostile to A549 malignant cell line in addition to the VEGFR-2 inhibition property. Compounds **1, 2** and **3** (**Fig. S8**) exhibited potential inhibitory potential countering to VEGFR-2 kinase in comparison to sorafenib control drug. Further these compounds were tested for the anti-tumor action over the malignant cell lines from different origins *viz*. OVCAR-3, Panc-1, HT29 and 786-O where compound **1** illustrated considerable cell death in most lines.

Hassan et al. (2021) documented synthesis of 33 new pyridine and fused pyridine derivatives *via* different chemical reactions. The resultant analogues were examined *in vitro* to assess anti-tumor action on two malignant cell lines, HepG2 (liver) and MCF-7 (breast) in comparison to the 5-fluorouracil (reference drug). Compounds **1, 2, 3, 4, 5** and **6** (**Fig. S9**) exhibited highest activity against both cell lines.

2.1.3. Synthetic pyridine derivatives exhibiting cytotoxicity

A novel synthetic platform has been developed by Behbehani et al. (2020) utilizing a new, convenient and efficient procedure to produce markedly substituted 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine systems. The initial cytotoxicity examination of these synthesized 10 pyridine derivatives were performed towards human malignant cell lines *viz*. A549 (lung cancer) and MCF-7 (breast cancer) by employing the MTT colorimetric test. The results revealed that the all 10 pyridine derivatives (**Fig. S10**) are potent cytotoxic agents as tested on MCF-7 and A549 malignant cells. Outcome of this study assures the possibility of the aforementioned compounds to serve as an appropriate primary source for future research in anticancer drug designing.

Suma and coworkers (Suma et al., 2020) accounted for designing and synthesis of 10 novel chalcone linked thiazole-imidazopyridine analogues library and characterized their structures *via* NMR (^{1}H and ^{13}C) and mass spectrometry investigations. Subsequently, all compounds were examined for the anticancer activity on four human malignant cell lines comprising breast carcinoma (MCF-7), lung carcinoma (A549), prostate carcinoma (DU-145) and breast carcinoma (MDA MB-231) by applying MTT procedure with etoposide as the positive control. Amongst all other compounds, compound **1** (**Fig. S11**) exhibited more strong anticancer action over all cancer cell lines upon comparison with the positive control.

Keshk and Izzularab (2021) reported designing, production, structural characterization, and anticancer assessment of cyanopyridines, pyridopyrazolotriazines and pyridopyra-

zolopyrimidines. Anticancer action of the compounds synthesized was ascertained *via* MTT assay over three cancer cell lines, *viz*., HepG-2 (liver cancer cell line), PANC-1 (pancreatic cancer cell line), A-549 (non-small lung cancer cell line) and normal fibroblast cells. 3-cyano-4,6-dimethyl-2-pyridone was used to synthesize an array of five 3-cyanopyridines, one pyridopyrimidine, six pyridopyrazolopyrimidines, one pyrazolopyridine salt and two pyridopyrazolotriazines. The compounds synthesized were tested *in vitro* for their anticancer action and their chemical structure elucidation was performed *via* the spectroscopic data and elemental analysis. Few of the compounds synthesized exhibited significant anticancer action; particularly one pyridopyrazolopyrimidine compound **(**Compound **1)** (**Fig. S12**) showed higher effectiveness to the control drug cisplatin on A-549 and was harmless to the normal fibroblast. Moreover, a pyridopyrazolotriazine compound (Compound **2**) (**Fig. S12**) exhibited the maximum activity amid the target compounds against HepG-2 while normal fibroblasts were kept safe.

2.2. Mode of action

Morak-Młodawska et al. (2021) reviewed phenothiazines substituted with the pyridine ring as potential anticancer molecules. Azaphenothiazines are the most diverse and well-studied class of modified phenothiazines, with a wide range of biological activity. Isomeric pyridobenzothiazines and dipyridothiazines, which are substituted azaphenothiazines with one and two pyridine rings, respectively, were also tested for anticancer efficacy against 10 cancer cell lines. Some 10-substituted dipyridothiazines and even 10-unsubstituted parent compounds, such as 10*H*-1,9-diazaphenothiazine and 10*H*-3,6-diazaphenothiazine, showed exceptionally powerful activity against cancer cell lines with IC_{50} values less than 1 g/mL and 1 M. The anticancer activity is determined by the tricyclic ring scaffolds as well as the substituents at the thiazine nitrogen atom. The kinds of cancer cell lines, the nature of tricyclic ring scaffolds with the position of the azine nitrogen atoms, and the mechanism of action have all been explored.

Since pyridine scaffold serve to be the potent anticancer targeting agents, Mohamed et al. (2021) reviewed the important biological targets like carbonic anhydrase (CA), proto-oncogene tyrosine protein kinase (ROS), c-Met receptor tyrosine kinase (RTK), EGFR (Epidermal growth factor receptor), cyclin-dependent kinase (CDK), PIM kinases, topoisomerases and the mode of action of pyridine analogs to generate anticancer response. Carbonic anhydrase inhibitors are inhibited by pyridines. Red blood cells, stomach mucosa, pancreatic cells, and even renal tubules contain carbonic anhydrase (CA), which is an essential enzyme. Acid–base balance, respiration, bone resorption, ureagenesis, gluconeogenesis, electrolyte secretion, and lipogenesis are all maintained by it. CA isoenzymes are key therapeutic targets in these processes, and they can be inhibited to treat a number of illnesses, including cancer. There are several connections between CA and cancer (Badger et al., 1994). CA IX and XII are the transmembrane isoenzymes discovered in tumor cells, and they are mostly prevalent in normal tissue with a little quantity in tumor cells. CA IX's involvement in cancer formation is linked to hypoxia, acidosis, and more (Pastorekova and Gillies, 2019). Pyidines also have anticancer action *via* working on ROS1 inhibitors (Tian et al., 2018), ALK/ROS1 dual inhibitors, and other pathways (Liu et al., 2019). The ROS1 gene encodes an enzyme known as proto-oncogene tyrosine protein kinase (ROS). It shares resemblance with the anaplastic lymphoma kinase protein (ALK). ROS1 has a function in healthy development, much like other physiological ligands. Pyridines have an effect on c-Met as well. The c-Met receptor tyrosine kinase (RTK) is a protein that is encoded by the MET gene and is known as the hepatocyte growth factor (HGF) receptor (Bottaro et al., 1991). Some pyridine scaffolds were identified to be type II c-Met inhibitors (Zhao et al., 2017). In addition to resistance, C-met plays a key role in the creation, spread, and advancement of a variety of malignancies. EGFR (Epidermal growth factor receptor) is another pyridine target which is a transmembrane receptor that helps cells to grow, survive, differentiate, and migrate. Misregulation of EGFR is linked to a variety of human illnesses, including cancer. As a result, blocking this route has shown to be an effective cancer therapy (Günther et al., 2019). Pyridines also act as a cyclin-dependent kinase (CDK) inhibitor. A group of serine/threonine kinases are known as CDKs. Their role in cell growth, development, proliferation, and death regulates the eukaryotic cell cycle. They are responsible for the cell cycle's synchronicity. CDK9 is a transcriptional regulator that regulates the production of anti-apoptotic proteins in cancer cells, allowing them to live forever. It interacts with a variety of transcription factors (TFs) and controls how they function. CDK9 inhibitors, which target both androgen receptor function and anti-apoptotic proteins, provide a unique and expanded therapeutic range compared to current therapy options (Asghar et al., 2015; Rahaman et al., 2016). PIM-1 kinase inhibitors are also affected by pyridines. PIM kinases are also Serine/threonine kinases and have 3 sub-types *viz*. PIM-1, PIM-2, and PIM-3. Many biological activities, including proliferation, differentiation, survival, and death, are connected to PIM-1 kinase. It also influences the progression and start of cancers including lymphomas, leukaemia, and solid tumors like the prostate, pancreas, and colon. As a result, inhibiting PIM-1 kinase is an essential target for cancer therapy (Mori et al., 2013). Pyridines also affect topoisomerases in another way. During the cell cycle, topoisomerases catalyse the breaking and rejoining of the phosphodiester backbone in DNA strands. Topoisomerase inhibitors are now utilized to treat cancer and bacterial infections. Topoisomerase inhibitors act as anticancer drugs by blocking the ligation process, which causes apoptosis and cell death by triggering single- and double-strand breaks that damage the whole genome (Murugavel et al., 2019).

3. Pyrimidine derivatives as anticancer agents (2019–2021)

Early in the organic chemistry history, pyrimidines were popular as "m-Diazine" resulting from the catabolism of uric acid. Alloxan was the first pyrimidine derivative isolated by Brugnatelli in 1818 during the oxidation of uric acid with nitric acid (Lagoja 2005). Like benzene and pyridine, pyrimidines also contain two nitrogen atoms at 1 and 3 positions of heterocyclic six- membered aromatic ring. Pyrimidine is a monochrome compound with melting and boiling points of 22.5 °C and 124 °C, respectively. Pyrimidines can also be isolated via nucleic acid hydrolyses mainly cytosine, thymine, and uracil. Pyrimidines correspond to an expansive category of com-

Table 2 Synthetic pyrimidine derivatives with anticancer activity.

Year	Author	Compound	*In vitro studies*	*In silico studies/ Possible targets*	Cell lines
Cell cycle regulatory activity					
2019	Ali et al.	Pyrazole and pyrazolo[1,5-a] pyrimidine derivatives	G_0-G_1 stage cell-cycle detention	CDK2/cyclin A2 enzyme inhibition	MCF-7, A549, HepG2 and Caco2
2019	El-Metwally et al.	4-(3,5-Dimethyl-1H-pyrazol-1-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine cyclic and acyclic analogues	Cytotoxicity, cell cycle inhibition, apoptosis stimulation	caspase 3, p53, TopoII	MCF-7, HepG2
2019	El-Metwally et al.	16 Thieno[2,3-d]pyrimidine analogues	G_2/M stage inhibition	Tyrosine Kinase, HER2 and EGFR	HepG2, HCT-116, A431 and MCF-7
2019	Metwally et al.	Derivatives of pyrazolo[1,5-a]pyrimidines	Cytotoxicity, cell cycle detention at G_2/M stage	PDB-ID: 5IVE	Hela, breast cancer
2019	Muthuraja et al.	Pyrazolopyrimidine derivatives	Cell cycle inhibition at metaphase	Eg5 inhibitor; ATPase allosteric sites	HeLa
2019	Yang et al.	Combretastatin A-4 (CA-4) analogues	G_2/M phase, anti-tubulin action	Tubulin polymerization inhibitors	A549, HeLa, HEK-293
2019a	Zhang et al.	Camphor-derived pyrimidine analogues	Anti-tumor action, G_0/G_1 stage, ROS-arbitrated mitochondrial apoptosis		MDA-MB-231, RPMI-8226, A549
2020	Abdelrazek et al.	1,5-Dihydropyrido-triazolo-pyrimidine analogues	Cell cycle regulation and meiosis	CK2	
2020	Eissa et al.	Pyrimidine-5-carbonitrile analogues	Anti-proliferative action at G_2M stage	Tyrosine kinase inhibitors of EGFR	HCT-116, HepG-2, MCF-7, A549
2020	El-Saidi et al.	Adenine 1 and Guanine 6 analogues	Cell cycle regulation	CDK-2 (cyclin-dependent protein kinase 2), BCL-2	BCL-2
2020	Farghaly et al.	4-Hetarylthiazoles (rigid chalcones) and thiazole-based chalcones	Cell cycle detention at the G_2/M stage, increase in the pre-G_1 apoptotic cells	Upregulation of Bax and downregulation of BCL-2	A549, HepG-2 and MCF-7
2020	Wang et al.	2,7-Disubstituted-thieno[3,2-d]pyrimidine derivatives	G_0/G_1 stage	Focal adhesion kinase (FAK) inhibitors	A-549, U-87MG and MDA-MB-231
2020	Zhang et al.	Triazolo-pyridazine/-pyrimidine derivatives	Cytotoxicity, G_0/G_1 phase	c-Met kinase	A549, HeLa, and MCF-7
Cytotoxic activity					
2019	Naagla et al.	Pyrimidine pyrazoline-anthracene analogues	Cell viability/cytotoxicity	Caspase 3/7	HepG2, Huh-7
2019	Amin et al.	6-Aryl-5-cyano-pyrimidine analogues		TS inhibitory activity, Bax/ BCL2	HePG-2, MCF-7 and HCT-116
2019	Farag and Fahim	Enaminonitriles based pyrazole analogues	Anticancer activity		MCF-7
2019	Huang et al.	Oxacalix[2]arene[2]pyrimidine analogues	Cytotoxicity and apoptosis		MCF7, HeLa, A549 and HepG2
2019	Salem et al.	Pyrimidine analogues via Cerium (IV) ammonium nitrate	Anti-tumor potential, cytotoxic activity		HePG-2, MCF-7, HCT-116 and PC3
2019	Shyyka et al.	Thieno[2,3-e][1,2,3]triazolo[1,5-a] pyrimidines and thieno[3,2-e][1,2,3]triazolo[1,5–a] pyrimidines	Cytotoxicity		NCI-60, SK-MEL-5
2019	Sobhy et al.	6,7-Dihydro-5H-cyclopenta[d]pyrimidine analogues		VEGFR 2 inhibition	
2019b	Zhang et al.	Hydroxamic acid moiety in a quinazoline-dependent PI3K pharmacophore	In vivo anti-tumor property	HDAC and PI3K dual inhibitors	HGC-27 and HCT116 xenograft models
2020	Ahmed et al.	Pyrimidine derivatives through polarized (e.g., Chalcone) heterocyclization		DHFR	HePG-2 and MCF-7

(*continued on next page*)

Table 2 (*continued*)

Year	Author	Compound	*In vitro studies*	*In silico studies/ Possible targets*	Cell lines
2020	Al-Rashood et al.	Thiazolopyrimidine derivatives		DNA binding	60 diverse cell lines
2020	Bakhotmah et al.	2-Fpyrano[2,3-c]pyrazoles-4-ylidenegmalononitrile backbone with pyridine, pyrazole, pyrimidine, chromone, diazepine, pyrano[2,3- d]pyrimidine, and pyrano[2,3-c] pyrazole systems	Cytotoxic actions		HCT-116, Hep-G2, and MCF-7
2020	Balupuri et al.	Pyrimidine-derived JAK3 inhibitors		Active sites of TYK2, JAK1 and JAK2, JAK3	
2020	Shakila Banu et al.	Pyrimidine analogues comprising pyrrole nucleus	Cytotoxicity		A549
2020	Ghoneim et al.	Analogues of pyrimidinone ring with five-membered heterocycles	Cytotoxicity	EGFR	PC-3, HepG-2, HCT116
2020	Goudzal et al.	Chain of azacalix [2] arene [2] pyrimidines analogues		CK2 protein kinase	
2020	Hosseinzadeh et al.	DHPM (3,4-dihydropyrimidine-2(1H)-one) and 2,6-diaryl-substituted pyridine analogues	Cytotoxicity	Kinesin Eg5 inhibition	MCF-7, AGS, HEK293
2020	Khalaf et al.	Substituted pyrimidines through glycosylation	Cytotoxicity		MCF-7, HepG2, RPE-1
2020	Li et al.	[1,2,3]Triazolo[4,5-d]pyrimidine derivatives	Cytotoxicity	LSD1 (Lysine specific demethylase 1), MAO-A/-B, kinases like BTK and CDK	
2020	Luo et al.	5-Methylpyrazolo[1,5-a]pyrimidine analogues	Cytotoxicity	c-Met kinase	MDA-MB-231, SH-SY5Y, HepG2 and A549
2020	Nolan et al.	Oxazolopyrimidines		VEGFR2 inhibitors	MDA-MB-231, OVCAR-3 and HCT-116
2020	Sekhar et al.	Thiazolo[3,2-a]pyrimidine hydrobromide analogues	Cytotoxicity	Topoisomerase-II	A549, MCF-7, HeLa and SKNSH
2020	Silbermann et al.	Pyrimidine analogues accompanying (a) halogen- and/or nitrogen-containing residues		ABCC1/ABCG2 inhibitors, ABCG2-mediated MDR	SN-38
2020	Yousif et al.	2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile 1 derivatives	Cytotoxicity		HT-29 and A-549
2021	Bommera et al.	1,2,4-Oxadiazole derivatives	Cytotoxicity		MCF-7, MDA MB-231, A549 and DU-145
Anti-tumorigenic activity					
2019	Fouda et al.	Pyrazole and pyrazolo[1,5-a] pyrimidine analogues	Anti-tumor activity		HCT-116, MCF-7, and HepG-2
2019	Li et al.	Triazole- fused pyrimidine analogues	Anti-proliferative action	LSD1/KDM1A inhibitors; CD11b and CD86	OCL-AML3, THP-1, K562 and U937, Raji
2020	Fatma et al.	Substituted chromeno[2,3-d]pyrimidine and chromenotriazolo[1,5-c]pyrimidine analogues	Anti-tumor action		MCF-7, HepG2
2020	Lakkaniga et al.	Pyrrolo[2,3-d]pyrimidine derivatives	Tumor cells migration	RET kinase	LC-2/ad cells
2020	Sakr et al.	Diphenyl-4-thioxo-1,4-dihydropyrimidin-5-yl) ethan-1-one	Antitumorgenic		MRC-5, A549
2020	Xie et al.	Ring-fused pyrazoloamino pyridine/pyrimidine analogues	Anti-proliferative action	Focal adhesion kinase (FAK) inhibitors	BXPC-3, MDA-MB-231, DU145, NCI-H1975 and 786O
2021	Singh et al.	Pyrimidine-based cationic amphiphiles (PCAms)	Anti-proliferative and anti-tubercular activity	MDR591	HeLa and KB-V1
2021	El-Sharkawy et al.	Thiophene, thienopyridine, Isooxazole, 2-pyridone analogues	Antitumorigenic		SF-268, MCF-7 and NCI-H460

Table 2 (*continued*)

Year	Author	Compound	*In vitro studies*	*In silico studies/ Possible targets*	Cell lines
Derivatives having inhibitory actions					
2019	Diao et al.	Pyrimidine-based benzothiazole analogues	CDK2 Binding	CDK2/cyclin A2 inhibition	HeLa, PC-3, HCT116, and MDA-MB-231
2019	Omar et al.	Triazolopyrimidines and sulfanylpyrimidines	Growth inhibitor	COX-2 inhibition	MCF-7
2019	Rahim et al.	Indole/isatin conjugated phenyl-amino-pyrimidine derivatives	BCR-ABL inhibition		K-562
2020	Asati et al.	Pyrazolo-pyrimidine derivatives	Serine/threonine kinase inhibition	PIM kinase barriers	

pounds, with substantial importance because of their broad array of biological properties as anti-cancer, anti-inflammatory, antiallergic, COX inhibitor, analgesic agents etc. (Gondkar et al., 2013).

Pyrimidine derivatives in medicinal chemistry have been recognized for their medicinal uses. Several pyrimidine analogues have been evolved as chemotherapeutic sources and are under excessive use. Substituted pyrimidines are synthesized and isolated from the flora, fauna, microbes, and marines for drug designing. A consolidated list of the diverse analogues is included in Table 2.

3.1. Classification of pyrimidine derivatives based on the biological action

3.1.1. Synthetic pyrimidine derivatives involved in cell cycle regulation

Ali et al. (2019) designed and synthesized an array of 19 unique pyrazole and pyrazolo[1,5-a] pyrimidine derivatives (**Fig. S13**) and checked the response on CDK2/cyclin A2 enzyme through *in vitro* studies. Compounds **1** and **2** inhibited the CDK2/cyclin A2 enzyme with inhibition check scores of 60% and 40%, correspondingly, standing them to be the most active. Conversely, compounds 3 and 4 were maximally active over the cell lines, MCF-7, A549, HepG2 and Caco2. Flow cytometric cell cycle assay results indicated compounds **3** and **4** to be inducing cell-cycle detention in the G_0-G_1 stage and resisting disintegration of DNA undergoing apoptosis. Molecular modeling investigation has also been conducted to acquire subsequent insight for the binding method of the intended compounds in conjunction with field configuration to characterize the analogous field attributes.

El-Metwally and coworkers (El-Metwally et al., 2019a) synthesized 4-(3,5-Dimethyl-1H-pyrazol-1-yl)-5,6,7,8-tetrahydro benzo[4,5]thieno[2,3-d]pyrimidine (**compound 1**) (**Fig. S14**) and conducted its functionally active reactions as nucleophile with different electrophilic agents by performing simplistic techniques to generate 16 diverse acyclic and cyclic analogues**.** The chemical structures of the created compounds were ascertained by the spectrometry data and molecular element studies. In addition to the parent compound **1,** analogues **4, 14, 16,** and **17** with IC_{50} at ~4–10 μM against MCF7 and HepG2 cell lines were preferred for subsequent investigations. Selectivity against cancer cell lines was ascertained *via* the high IC_{50} values (> 60 μM) opposed to WI38 (normal fibroblasts). Analogues **4, 14,** and **17** stimulated the p53 expression approximately by 3–4 times. All analogues triggered a rise in the expression of caspase 3 and an increase in cleaved caspase 3 actions. An increase in the caspase 3 expression by compound **1** and analogue **16** was not complemented by rise in expression of p53 or reduced caspase 3 actions. Caspase 3 may directly be acted upon by these two thienopyrimidines. Analogue **17** exclusively reduced the expression of topoisomerase II (Topo II) by about 60%. The molecular docking study exhibited analogues **4** and **17** acquired high binding energies capable of binding and inhibiting Topo II. In compliance with the docking representation, analogues **4** and **17** decreased the concentration of Topo II respectively by 82 and 90% with respect to the untreated cells. Nevertheless, the parent compound **1** too produced a considerable 34% diminution in the enzyme concentration even though it was not envisaged as an enzyme ligand in the docking investigation. Altogether, analogues **4, 14** and **17** (**Fig. S14**) illustrated selective cytotoxicity, possibly through cell cycle inhibition, apoptosis stimulation. Moreover, they might function as cytostatic agents by restraining Topo II.

Kinases deregulation is directly attributed to cancer progression and the tyrosine kinase family is one of the key players in recent cancer treatment procedure. So, Elmetwally et al. (2019b) generated 16 thieno[2,3-*d*]pyrimidine analogues to asses them as HER2 and EGFR tyrosine kinase inhibitors. The compounds were assessed *in vitro* for their inhibiting actions countering to $EGFR^{WT}$; and the most effective compounds exhibiting potent IC_{50} values in respect to $EGFR^{WT}$ were subjected *in vitro* analysis for their inhibitory roles against mutant HER2 and $EGFR^{T790M}$ kinases. Furthermore, the anti-tumor behavior of these compounds was analyzed over HepG2, HCT-116, A431 and MCF-7 cancer cell lines. Maximal activity against the explored cell lines was exhibited by the compounds **1, 2** and **3** (**Fig. S14**) in comparison to the erlotinib control. Ultimately, the most active anti-tumor compound **3** was chosen for downstream studies to ascertain its impact on the cell cycle and apoptotic mechanism in MCF-7 cell line. The results suggest that this compound inhibits G_2/M stage of the cell cycle and is a competent apoptotic mediator. Lastly, molecular docking investigations demonstrated a proficient binding model of the lab created compounds with the potential target, $EGFR^{T790M}$ and $EGFR^{WT}$.

Metwally et al. (2019) synthesized a new chain of pyrazolo [1,5-a]pyrimidines and ascertained *via* elemental and spectral analysis. Some chosen compounds from the series were tested for the cytotoxic action on Breast MCF-7 and Hela malignant

cell lines through MTT assay. Compounds **1, 2** and **3** (**Fig. S15**) displayed the greater cytotoxic activity opposed to the two cancer cell lines taking doxorubicin as a control drug. The most effective cytotoxic compounds **1, 2** and **3** offered inhibitory action over histone lysine demethylases (KDM). The most active KDM inhibitor, compound **2** was observed to instigate cell cycle detention at G2/M stage by 4 times with respect to the control and stimulated total apoptotic effect, 10 times greater than control. Lipinisk's rule of five was applied while performing *in silico* experiments on the cytotoxically active compounds **1, 2** and **3**. Additionally, molecular docking investigation was exploited to discover the mechanism of binding of actively cytotoxic compounds to enzyme. Furthermore, some *in silico* analysis was conducted for analogues **2** and **3** through Swiss ADME.

Considering the fact that human kinesin Eg5 being promising inhibitory site used in cancer chemotherapy by Muthuraja et al. (2019) reported pyrazolopyrimidine derivatives as active Eg5 inhibitor preventing the mitotic kinesin development. Metaphase obstruction *via* attachment of foreign inhibitors to Eg5 ultimately directs to apoptosis. IC_{50} values were estimated in contrast to the Eg5 motor domain utilizing ATPase steady-state analysis. For enhanced comprehension, molecular docking simulation was also performed. The docking simulation results suggest interactions of the projected inhibitors with both the two allosteric site positions *viz*. helices α4 & α6, and helices α2, α3 and loopL5. Three pyrazolopyrimidine analogues (**1, 2** and **3**) (**Fig. S16**) from fifteen exhibited considerable Eg5 inhibition. These three analogues were assessed for their *in-vitro* anti-proliferative action over the HeLa (cervical cancer cell line).

Yang et al. (2019) as restricted combretastatin A-4 (CA-4) analogues, a new array of [1,2,4]triazolo[1,5-a]pyrimidines acquiring 3,4,5-trimethoxylphenyl groups has been productively attained by means of a proficient one-pot three- element reaction of 3-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazol-5-amine, aldehyde and 1,3-dicarbonyl compounds. Preliminary biological studies established selected synthesized compounds exhibited potential *in vitro* anti-tumor action counter to three cancer cell lines. Amid them, the exceedingly active derivative **26** reduced the progression of A549, and HeLa cell lines, suggesting exceptional selectivity on the HEK-293 non-tumor cell line indicating that the aimed compounds may possibly acquire a high safety index. Furthermore, cell cycle study demonstrated that the derivative **26** considerably increased HeLa cells detention in G_2/M phase, temporarily the compound may radically influence cell microtubule networks and morphology. Additionally, compound **28** demonstrated strong anti-tubulin action and molecular docking investigation identified that the derivative occupied the tubulin's colchicine-binding site. These interpretations indicate [1,2,4]triazolo[1,5-a]pyrimidines correspond to a novel tubulin polymerization inhibitors class aiming further studies to create potent anticancer agents.

Emphasizing the importance of polypharmacology in modern drug discovery, Zhang et al. (2019a) revealed formation of 49 new HDAC and PI3K dual inhibitors in which zinc binding functional group was introduced as the hydroxamic acid moiety to a quinazoline-dependent PI3K pharmacophore by means of a suitable linker. Compounds **1** and **2** (**Fig. S17**) turned out to be the lead compounds as established by methodical SAR (structure – activity relationship) investigations that concurrently inhibited HDAC and PI3K. Nanomolar potencies and promising anti-proliferative action was also exhibited by these compounds in addition to efficient modulation of p-AKT and Ac-H3 expression, cell cycle arrest, and apoptosis induction in HCT116 malignant cells. Moreover, compound **1** was tested in HGC-27 and HCT116 xenograft models to prove substantial *in vivo* anti-tumor property exhibiting cancer growth retardations of 62.6%, and 45.8% respectively. On the whole, this work demonstrates assurance in determining novel anticancer remedies by the targeting simultaneous HDAC and PI3K pathways as the line of attack with a single molecule.

Abdelrazek et al. (2020) prepared a new chain of 1,5-dihydropyrido-triazolo-pyrimidine analogues (**Fig. S18**) through cyclocondensation of chalcone and 6-aminothiouracil reaction products, the 2-thioxo-pyrido[2,3-d]pyrimidines with various hydrazonoyl chlorides. On the basis of spectroscopic studies the chemical synthesis and the configurations of the newly formed compounds were revealed. Marked compounds were subjected to docking utilizing MOE 2014.010 software package. Newly formed compounds targeted CK2 (Human Cyclin-defendant Kinase 2) because of imperative function to regulate the human cell cycle and meiosis.

Eissa et al. (2020) designed a novel series of pyrimidine-5-carbonitrile analogues which serve as ATP pretending tyrosine kinase inhibitors of EGFR (epidermal growth factor receptor). These analogues were produced and assessed for the *in vitro* cytotoxicity properties countering to a group of four human malignant cell lines *viz*; HCT-116 (colorectal carcinoma), HepG-2 (hepatocellular carcinoma), MCF-7 (breast cancer), and A549 (non-small cell lung cancer cells). Five target analogues (**Fig. S19**) were found exhibiting average anti-proliferative action against the cell lines under consideration and proved more effective in comparison to the EGFR inhibitor, erlotinib. Particularly, compound **1** demonstrated 4.5 to 8.4 times more erlotinib action over HCT-116, MCF-7, A549 and HepG-2 cells. Furthermore, the highly cytotoxic analogues which showed potent IC_{50} values opposed to the four malignant cell lines were processed for future studies to validate their kinase inhibition properties on $EGFR^{WT}$ and $EGFRT^{790M}$ using HTRF (homogeneous time resolved fluorescence) assay. Analogue **1** proved to be the most potent towards both $EGFR^{WT}$ and $EGFRT^{790M}$. The cell cycle and apoptotic investigations suggested the ability of compound **1** to seize the cell cycle at G_2/M stage and stimulate considerable apoptosis in HepG-2, HCT-116, MCF-7cells. Moreover, compound **1** increased the caspase-3 level by 6.5 times in HepG-2 cell line in comparison to the control. Lastly, docking analysis was conducted to investigate the binding process of the synthesized analogues against the projected targets; $EGFR^{WT}$ and $EGFR^{T790M}$. Further computational ADMET analyses were conducted to investigate drug- resemblance attributes.

El-Saidi et al. (2020) in their study reported synthesis of new compounds **1** and **2** incorporating DNA bases for example- Adenine 1 and Guanine 6 analogues. Facile protocols to produce compounds **1** and **2** were applied utilizing pyrimidine as a substituted DNA base ring. An alternative plan for synthesis of novel yet simple pyrimidine rings exploiting ethylcyano acetate and thiourea to afford 6-amino-2-thiouracil was implemented. The reaction of thiouracil 10 with chloro ester or chloro cyano and ketone, lead to the creation of four adduct compounds. All the newly produced compounds were analyzed *via* docking studies, to get an overview of their

binding modes opposed to CDK-2 (cyclin-dependent protein kinase 2) that profoundly regulates cell cycle and receptor protein BCL-2 (B-cell lymphoma 2) of cell apoptotic cycle. These objected compounds were chosen on the basis of their significant functions in cancer development by means of cell cycle regulation and DNA replication. Molecular-docking results revealed that analogue **4** (**Figure S20**) was the most appropriately docked ligand countering both targets, as it exhibited the least binding energy, critical hydrogen bonding and hydrophobic connections with the targets.

Understanding the crucial requirement for novel antitumor molecules acquiring high selection rate for cancer cells encouraged Farghaly et al. (2020) to create an array of new 4-hetarylthiazoles (rigid chalcones) and thiazole-based chalcones. The making of 4-hetarylthiazoles and thiazolyl chalcones with affirmation of their chemical structure has been explained clearly. The anti-tumor property of these analogues was anticipated countering to A549, HepG-2 and MCF-7 human malignant cell lines. Chalcone derivative 1 (3-(4-Meth oxyphenyl)-1-(5-methyl-2-(methylamino) thiazol-4-yl)prop-2-en-1-one) exhibited considerable and wide-ranging antitumor action which was more effective than the control, *Doxorubicin*. Additionally, analogues **2, 3** and **4** (**Fig. S21**) demonstrated strong activity in comparison to *Doxorubicin*. Moreover, these analogues had lower toxicity over WI-38 (normal lung cells) with elevated selection index. Subsequent studies on compound **1** concerning its impact over the regular cell cycle profile in A549 cells revealed cell cycle detention at the G_2/M stage in addition to increase in the pre-G1 apoptotic cells percent. CDK1/CDK2/CDK4 inhibition tests were performed on compounds **1, 2, 3** and **4** and the outcomes suggested nondiscriminatory restrain on the analyzed CDKs. Furthermore, docking investigation envisaged that compounds **1**–**4** may fit into CDK1 enzymes' the ATP binding site. Compounds **1**–**4** were also tested for their apoptotic stimulation potential anticipated against some apoptotic markers. Interestingly, they were also capable of increasing expression levels of Bax by 6.36–10.12 times and decreased Bcl-2 expression by 1.94–4.12 times in comparison to the control. Besides this, a rise in level of operational caspases; caspase-3 and p53 by 8.76–10.56 and 6.85–10.36 times, respectively was experiential which was greater than the control indicating their ability to stimulate apoptosis.

Wang et al. (2020) designed and synthesized an array of 2,7-disubstituted-thieno[3,2-d] pyrimidine derivatives which were examined as new focal adhesion kinase (FAK) inhibitors. The fresh 2,7-disubstituted-thieno[3,2-d] pyrimidine skeleton has been created as a novel kinase inhibitor stage that imitates the bioactive molecular arrangement of the distinguished diaminopyrimidine motif. Majority of the compounds effectively concealed the FAK enzymatic activities and strongly inhibited the A-549, U-87MG and MDA-MB-231 cancer cell lines proliferation. Amid these analogues, compound **1** (**Fig. S22**) exhibited efficient inhibition of the enzyme and demonstrated stronger potential than TAE-226 in A-549, U-87MG and MDA-MB- 231 cells. Compound **1** also showed comparatively less cytotoxic action towards HK2, a normal human cell line. Consistent with the flow cytometry outcome, compound **1** stimulated the MDA-MB-231 cells apoptosis in a dose- dependent manner and efficiently detained MDA-MB-231 cells during G_0/G_1 stage. Further studies made clear that compound **1** actively suppresses the MDA-MB-231 cells migration. All together, these data keep up the subsequent expansion of compound **1** as a head compound for FAK-objected anticancer drug exploration.

Zhang et al. (2020) planned and synthesized two new series of triazolo-pyridazine/-pyrimidine derivatives and tested *in vitro* their inhibitory action over c-Met kinase, in addition to three cancer cell lines *viz.,* A549, HeLa, and MCF-7 (c-Met overexpressed malignant cell lines) and one normal cell line LO2 (normal human hepatocytes). The pharmacological data revealed that majority of the tested compounds exhibited mild cytotoxicity, and the most potent compound **1** (**Fig. S23**) demonstrated considerable cytotoxicity over MCF-7, A549, and HeLa cell lines. Furthermore, the inhibitory action of compound **1** countering c-Met kinase was nearly equal to that of Foretinib. The outcome of the AO (acridine orange) single staining test revealed that compound **1** could astonishingly stimulate A549 cells apoptosis. The apoptosis results and cycle allocation of cells demonstrated that compound **1** might trigger late apoptotic action in A549 cells and accelerate A549 cells arrest in the G_0/G_1 phase. SARs (structure − activity relationships), pharmaceutical testing results, and docking analysis suggested that presenting 5-methylthiazole part to the five-atom moiety was useful for the action. As yet, the presented data revealed that compound **1** might become a potent class II c-Met inhibitor.

3.1.2. Synthetic pyrimidine derivatives exhibiting cytotoxicity

In an effort to rise above the cancer cell resistance Naglaa and coworkers (Naglaa et al., 2019) designed and synthesized a new series of 20 PPADs (pyrimidine pyrazoline-anthracene analogues). Resazurin *in vitro* assay was performed to screen the anti-liver cancer action of the synthesized compounds on two HCC (hepatocellular carcinoma) cell lines, HepG2 and Huh-7, in comparison to normal fibroblast cells. Broad-spectrum anticancer activity was exhibited by the 20 PPADs against the aforementioned cell lines demonstrating major impact on malignant cells when compared to normal cells. High potency of compound **1** was recorded against HepG2 and Huh-7 cell lines with respect to control doxorubicin (DOX) activities. According to the conducted SAR (structure activity relationship) compounds **1, 2, 3,** and **4** (**Fig. S24**) were observed to be the most potent anticancer agents inducing apoptosis in HepG2 and Huh-7 cells *via* significant upregulation of caspase 3/7 at all studied concentrations. This investigation suggested that compound **1** could be an effective anticancer drug.

Considering cancer as a challenging and perplexing problem, Amin and coworkers (Amin et al., 2019) designed and synthesized an array of ten 6-aryl-5-cyano-pyrimidine analogues and assessed their anticancer action opposed to HePG-2, MCF-7 and HCT-116 cell lines. High anticancer activity was exhibited by compounds **1**–**8** in comparison to 5-fluorouracil. Later, the compounds demonstrating the potent anticancer action were evaluated for their capacity to obstruct the enzyme thymidylate synthase (TS). All the studied compounds got verified to acquire a marked TS inhibitory activity. Besides this, apoptotic investigations were carried out on the most effective compound **7** (**Fig. S25**) for testing the proapoptotic ability. Interestingly, compound **7** increased the active caspase 3 levels, and raised the Bax/Bcl2 proportion by 44 times in contrast to the control. Ultimately, a molecular dock-

ing experiment was conducted to observe the possible relations between the compounds in action and the active site of thymidylate synthase enzyme.

Farag and Fahim (2019) explored the efficacy of the two enaminonitriles for synthesizing pyrazole analogues **1a,b, 2a, b**, diaminopyrimidine analogues **3, 4**, pyrazolo[1,5-a] pyrimidines **5, 6** triazolo[4,3-a]pyrimidines **7, 8** imidazo[1,2-a] pyrimidine analogues **9** and **10** in their investigation (**Fig. S26**). Majority of the created compounds demonstrated exceptional *in vitro* anticancer action against the cell line MCF-7. SAR (structure–activity relationship) was employed to link up the biological action with the suitable quantum for instance total energy. Mulliken atomic charges and energy of the LUMO and HOMO were also estimated.

Huang et al. (2019) synthesized 15 new oxacalix[2]arene[2] pyrimidine analogues and evaluated for the anti-tumor activity against MCF7, HeLa, A549 and HepG2 human cancer cell lines *via* an MTT assay. Certain compounds demonstrated substantial anti-proliferative action against the human cancer cell lines. Strongest inhibitory action was performed by the compound **1** (**Fig. S27**), containing an ethanolamine moiety against HepG2. Additionally, a cell apoptosis evaluation suggested that the antineoplastic property of compound **1** might be accredited to its potential of apoptosis stimulation.

Salem et al. (2019) reported a simple yet effective one-pot eco-friendly production of pyrimidine analogues *via* the recyclable CAN (Cerium (IV) ammonium nitrate) catalyst and water being the base. Spectral and elemental analyses proved to be the basis of structure elucidation of the newly synthesized compounds. Furthermore, selected analogues of the products were evaluated to assess their anti-tumor potential over four cancer cell lines (HePG-2, MCF-7, HCT-116 and PC3) through MTT test and the outcome revealed potent cytotoxic activity in some of these compounds, as indicated by the IC_{50} values. 3D pharmacophore model was generated in the molecular modeling investigation. The study was in coherence with the experimental data.

Shyyka et al. (2019) performed *in vitro* study to establish the anticancer action of organically synthesized thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*] pyrimidines and thieno[3,2-*e*][1,2,3]triazolo[1,5 *a*] pyrimidines (**Fig. S28**) *via* MTT test and spectrophotometric analysis. The isomeric thienotriazolopyrimidine analogues were investigated for their anti-tumor action in the NCI-60 malignant cell line. The discerning effect of 5-oxo-4,5,6,7,8,9-hexahydrobenzo[4,5]thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine-3-carboxamide over SK-MEL-5 (melanoma cell line) was experiential. Two compounds demonstrated a considerable action on breast cancer cells as well as CNS. Some thienotriazolopyrimidines acquired anti-tumor action with a particular result on an individual cell line. These results prove to be significant for subsequent structural standardization for increasing selection and anticancer action of fused pyrimidines.

Sobhy et al. (2019) planned to synthesize and evaluate an array of new 6,7-dihydro-5H-cyclopenta[d]pyrimidine analogues as a novel chemical scaffold acquiring VEGFR 2 (vascular endothelial growth factor receptor) inhibitory action. Compounds **1** and **2** (**Fig. S29**) correspondingly demonstrated enzyme inhibitory activity of 97% and 87% and showed promising dose dependent VEGFR 2 blocking. Consecutive molecular modelling methods were applied to create 6,7-dihydro-5H-cyclopenta[d]pyrimidine scaffold preceding the production and biological assessment of the analogues. At first, sorafenib docking at the binding position of VEGFR 2 was performed to investigate its binding inclination and similarity, after that a suitable 3D QSAR pharmacophore model was generated for application in the virtual selection of diverse 3D databases. Chemical configurations with potential pharmacophore-dependent virtual inspection outcomes were processed using molecular docking analyses in the VEGFR 2 binding site. A new scaffold was created by assimilating the outcomes of the generated pharmacophore model and docking investigation. The newly designed scaffold exhibited non-polar connections with the overlooking compartment of kinase which might be related to rising residence time in VEGFR 2, which is an important accomplishment feature for ligand standardization in drug development. Diverse analogues of the new scaffold were established *via* docking investigations and pharmacophore tracing, through which they demonstrated potent outcomes as VEGFR 2 inhibitors to be produced and naturally assessed. 6,7-dihydro-5H-cyclopenta[d]pyrimidine is a novel scaffold which could be additionally standardized to produce active VEGFR 2 inhibitors.

Zhang et al. (2019b) synthesized, 24 new camphor-derived pyrimidine analogues; and determined their structures using regular methods and further single crystal XRD analysis was performed to confirm compound **1** (**Fig. S30**). The cytotoxicity of the aimed compounds over a panel of GES-1 (human normal) and MDA-MB-231, RPMI-8226, A549 cancer cell lines was analysed through MTS assay. It got revealed that compound **3f** demonstrated the highest anti-tumor action, in comparison to etoposide, and had very low cytotoxic activity over the normal GES-1 cells with respect to the reference drug. Successive mechanism investigation in MDA-MB-231 cells suggested that compound **1** captures G_0/G_1 stage and conducts apoptotic process in a dose dependent manner. In addition, the deficit of mitochondrial membrane potential and improvement of cellular ROS levels were also recorded upon compound **1** treatment, which inferred that compound **1** demonstrated cytotoxic action by a ROS- arbitrated mitochondrial apoptosis pathway. This result was substantiated by a considerable rise in the pro-apoptotic proteins expression like cytochrome C, Bax, and caspase-3, and reduction of anti-apoptosis Bcl-2 protein. On the whole, compound **1** could be taken up for further studies in the expansion of anti-tumor agents of natural origin.

Ahmed et al. (2020) reported the production of 13 new pyrimidine derivatives achieved through polarized system (e.g. Chalcone) heterocyclization. Chalcone 3 was produced by the Claisen-Schmidt condensation of 2-acetyl naphthalene with 4-(N, N-dimethylaminobenzaldehyde) (**Fig. S31**) which was used to synthesize different pyrimidine analogues by reaction with thiourea, urea, and guandine hydrochloride prepared in the solution of ethanolic sodium hydroxide. The reaction potential of the newly produced pyrimidine analogues in relation to diverse electrophilic and nucleophilic reagents was investigated. Structural elucidation of the synthesized pyrimidine analogues were established through elemental and spectral studies. All the target analogues were tested *in vitro* on HePG-2 and MCF-7 cell lines for their anticancer actions. Some of them acquire a broad spectrum medicinal property. Lastly, docking analysis was carried out to show the possible association with the active site of DHFR (dihydrofolate reductase).

In a research performed by Al-Rashood et al. (2020), 26 novel thiazolopyrimidine derivatives were produced as purine analogs. Spectroscopic methods like NMR and mass spectrometry were used to validate the configuration of the formed products. Additionally, the analogues newly synthesized were assessed for their anti-tumor activity following NCI selection method countering 60 diverse cell lines as a part of 9 different panels. Moreover, the analogues were tested for the DNA binding property. The outcomes indicated that compound **35** verified to be the potently active constituent of the target series and it is endorsed to the 5-dose study where it provides TGI, GI50 and LC_{50} values of 6.61, 1.07, 34.7 μM respectively. Besides this, it was also established to acquire a superior DNA binding action comparable to that created by doxorubicin which acts as a positive control. Additionally, compound **1** was confirmed to be the most potent DNA binding agent having the binding affinity of 28.38 ± 1.1. The pharmacokinetic attributes were also estimated. Binding manner of compounds **1** and **2** (**Fig. S32**) to minor groove of DNA through hydrogen bonding was studied using molecular docking experiments. Thus, correlating anticancer property of compounds **1** and **2** to DNA binding.

Bakhotmah et al. (2020) utilized novel molecular frames to carry out a facile and effectively catalyzed heterocyclization reaction to assemble blocks of promising bioactive 2-fpyrano [2,3-c]pyrazoles-4-ylidenegmalononitrile backbone combined with pyridine, pyrazole, pyrimidine, chromone, diazepine, pyrano[2,3- d]pyrimidine, and pyrano[2,3-c]pyrazole systems. The method relied on action of 6-amino-4-(4-oxo-4H-chro men-3-yl)-3-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbo nitrile (1) with diverse protonated carbon and nitrogen in alcoholic sodium ethoxide and probable reaction system was also recommended. Configuration of the identified products was validated through elemental studies and spectral methods and was also assayed to prove cytotoxic actions. Amongst the compounds synthesized, both **1** and **2** (**Fig. S33**) demonstrated to acquire strong cytotoxic actions against all tested cancer cell lines.

Janus kinase 3 (JAK3) is a potential drug used in the therapy of autoimmune diseases, organ transfer refutation, inflammatory diseases, and different malignancies. In the research conducted by Balupuri and coworkers (Balupuri et al., 2020), docking, MD simulation, 3D-QSAR and MM/PBSA investigations were conducted on an array of pyrimidine-derived JAK3 inhibitors. A dependable COMSIA model was created and verified using peripheral confirmation test group, bootstrap, advanced mix up and r^2m grade studies. Structural necessities recognized by means of model contour maps were exploited to computational designing of 170 novel JAK3 barriers with enhanced strength. Docking analysis was carried over the chosen records and recently produced analogues to demonstrate their binding method and to recognize significant associating residues within the JAK3 active spot. Additionally, docking results of the preferred compounds contained by the active sites of TYK2, JAK1 and JAK2 pointed to their JAK3 selectivity. Further investigation of the binding interactions was encouraged *via* the molecular docking replications (100 ns) over the docked composite of compound **1** (most active compounds of the data set) (**Fig. S34**). Some critical amino acid residues like Lys_{830} (glycine-rich loop), Ala_{853}, Leu_{905} (hinge region), Cys_{909}, Asn_{954}, Leu_{956} and Ala_{966} were recognized. Hydrogen bond relation with hinge residue Leu_{905} was crucial to attachment of JAK3 barriers. Furthermore, MM/PBSA computation offered the free binding energy of the compound **1**. The intended molecules exhibited potential outcomes in the primary computational ADMET studies. Results of this investigation could additionally be utilized to build up promising JAK3 inhibitors.

Shakila Banu et al. (2020) targeted this study for synthesis, characterization and evaluation of the anticancer potential of novel pyrimidine analogues as the main objective. The current investigation was commenced to produce pyrimidine analogues comprising pyrrole nucleus. The compounds 4-[aminomethyl]-*N*-(4-methyl-3-{[4-(1*H*-pyrrol-2-yl) pyrimidin-2-yl]amino}phenyl) benzamide (compound 1) and 4-[(propylamino) methyl] - *N*- (4- methyl − 3 - { [4- (1*H*- pyrrol- 2-yl) pyrimidin- 2 -yl] amino} phenyl) benzamide (compound **2**) were made by standard procedure. All the compounds synthesized were validated through spectral methods like- IR, NMR and MS. The target analogues got assessed for the anticancer potential *in vitro* over A549 cell line (non-small cell) using MTT test. Characteristic peaks of all the target compounds were observed in FTIR, ^{1}H NMR and Mass spectral studies. *In vitro* anticancer potency of compounds **1** and **2** indicated high potential with respect to the control drug sunitinib. Designing and synthesis of new pyrimidine analogues by traditional method and good anticancer action of the compounds **1** and **2** amid all derivatives recommended the possibility of these compounds to be developed as potent anticancer agents.

Ghoneim et al. (2020) designed and prepared new analogues of pyrimidinone ring hauling few five-membered heterocycles. 1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6- methyl-N0-((naphthalen-4-yl) methylene)-2-oxopyrimidine-5-carbohydra zide was reacted with thioglycolic acid to produce 1,3-Thiazolidin-4-one derivative (Compound **1**). Reaction product of hydrazide and benzoyl chloride got cyclized to 1,3,4-oxadiazole (compound **2**) through phosphorus pentoxide. Likewise, the pyrazole derivative (compound **3**) was produced by the reaction of hydrazide and ethyl acetoacetate. Moreover, reacting phenyl isothiocyanates and hydrazide generated carbothioamide that upon reflux with hydrazonoyl chloride yielded 1,3,4-thiadiazole analogue (compound **4**). Additionally, reaction of carbothioamide 11 and sodium hydroxide with subsequent methylation through methyl iodide led to the formation of 1,2,4-triazole derivative (compound **5**). The structure elucidation of the newly synthesized heterocyclic compounds was carried out *via* elemental and spectral analysis. The cytotoxicity of the compounds (**1**–**5**) (**Fig. S35**) under this study was determined *in vitro* countering to the three malignant cell lines *viz*., prostate adenocarcinoma (PC-3), liver carcinoma (human HepG-2), and colorectal carcinoma (HCT116) by MTT assay. All the target compounds emerged to acquire elevated inhibition levels against HCT116, and PC-3 cell lines, whereas acquired weak inhibition levels opposed to HepG-2 cell lines, particularly, the thiadiazole derivative **14**. Moreover, docking analysis was performed on compounds **1**–**5** targets inside EGFR as a supposition for the anticancer property. All the docked analogues exhibited good fit with EGFR recorded docking scores range.

Goudzal et al. (2020) performed QSAR (quantitative structure–activity relationship) studies applying anticancer action approach over a chain of azacalix [2] arene [2] pyrimidines analogues (**Fig. S36**). MLR (multiple linear regressions) and MNLR (multiple nonlinear regressions) statistical analyses

were utilized to produce the non-linear and linear 2d-QSAR models, based on computed descriptors by means of the DFT (density functional theory) (B3LYP/6-31G) achieved using chemsketch, GaussView, and chemoffice softwares. The preferred model was examined by the internal/external validation and Y-randomization. In addition to 2D-QSAR system, molecular docking studies revealed that the compound chosen for the docking has a righteous affinity towards the CK2 protein kinase.

Considering cancer as one of the major global health issues, Hosseinzadeh et al. (2020) synthesized DHPM (3,4-dihydropyrimidine-2(1H)-one) and 2,6-diaryl-substituted pyridine analogues as potent anti-tumor structures and assessed their cytotoxic activity over numerous cancer cell lines. A facile and useful process was accounted to produce these derivatives, utilizing magnetic cobalt ferrite ($CoFe_2$ O_4 @SiO_2 -SO_3H) nanoparticles under solvent-free conditions and microwave irradiation. The structural attributes of the synthesized nanocatalyst were studied through XRD, SEM, FTIR and TGA methods. *In vitro* cytotoxic impact of the prepared products was tested against MCF-7 (human breast adenocarcinoma), AGS (gastric adenocarcinoma), and HEK293 (human embryonic kidney) cell lines *via* MTT assay. The results revealed that DHPM derivative (compound 1) was the most cytotoxic molecule for the MCF-7 cell line. Furthermore, other DHPM derivatives (compounds **1** and **2**) (**Fig. S37**) exhibited exceptional cytotoxic properties against the AGS cell line. Even though they are pyridine analogues, compounds **3** and **4** (**Fig. S37**) were more efficient on the cell line MCF-7. Results indicated that the target analogues displayed low cytotoxic potential over HEK293 cells. Molecular docking was performed to evaluate the kinesin Eg5 inhibition ability of the target compounds. The docking results indicated that, amid pyridine analogues, compound **4** acquired the highest free energy of binding (–9.52 kcal/mol) and least Ki (0.105 μM), and amongst the pyrimidine analogues, compound **1** had the highest free energy of binding (–7.67 kcal/mol) and least Ki (2.39 μM). Maps of ligand-enzyme affinity demonstrated that compounds **1** and **4** possess the ability to interact with the Eg5 binding site through H-bonding to amino acid residues, GLU116 and GLY117. The outcome of this investigation strongly recommends inhibitory potential of DHPM and pyridine derivatives against significant tumorigenic properties of gastric and breast cancer cells. The results may prove to be helpful in the consequent designing of DHPMs and pyridine derivatives as promising anticancer agents.

Khalaf et al. (2020) linked novel 1,3,4-thiadiazole thioglycosides to synthesize substituted pyrimidines through glycosylation of 1,3,4-thiadiazole thiol compounds. In addition, new 1,2,3-triazole derivatives associated to carbohydrate units were synthesized utilizing normal chemistry parameters executing the azidealkyne cycloaddition of substituted-aryl-azides catalyzed by Cu(I) choosing alkyne-functionalized sugars. The structure elucidation of the novel analogues was established through different spectroscopic methods, like ^{1}H NMR, ^{13}C NMR, IR and elemental analyses. The cytotoxicity of the synthesized analogues was assayed *in vitro* in opposition to HepG-2 (human liver cancer) and MCF7 (human breast adenocarcinoma) cell lines.

Keeping in view the fact that LSD1 (Lysine specific demethylase 1) has a vital function in sustaining a stable methylation condition at histone tails, Li et al. (2020) intended and evaluated two novel sequence of [1,2,3]triazolo[4,5-d]pyrimidine derivatives including (thio)urea moiety. Since overexpression of LSD1 is accompanies emergence of various cancers, the newly synthesized derivatives were tested for their LSD1 inhibitory properties. Amid them, compound **1** (**Fig. S38**) exhibited moderate LSD1 inhibitory action, as well as elevated the H3K4me2 expression levels at the cellular level. This compound also demonstrated high selectivity in counter to MAO-A/-B, plus a panel of kinases like BTK and CDK. Furthermore, the MTT assay recommended that the chosen compounds may inhibit the LSD1-overexpressed cancer cells proliferation. Even if, this class of compounds merely demonstrated mild anti-LSD1 action in the micromolar limits, this study imparts a new LSD1 inhibitor chemotype with superior enzyme selectivity in addition to cellular LSD1 inhibitory role and could offer a purposeful model in developing more effective LSD1 inhibitors for cancer therapy.

Luo et al. (2020) designed, synthesized, and tested 24 new 5-methylpyrazolo[1,5-*a*] pyrimidine analogues for their inhibitory properties *in vitro* over c-Met kinase and antitumorigenic action over the MDA-MB-231, SH-SY5Y, HepG2 and A549 cell lines. Majority of the analogues astonishingly checked c-Met kinase activity and exhibited medium to high-quality cytotoxic action and selectivity enrouting four malignant cell lines. Amongst them, analogues **1** and **2** (**Fig. S39**) were found to be the highly promising preferentially c-Met inhibitors and exhibited repression capacity as good as that of the standard cabozantinib. Cell proliferation evaluation subsequently established cytotoxic properties and selection of the two significantly potent analogues **1** and **3** (**Fig. S39**) against MDA-MB-231 cells. Analogues **2** and **4** (**Fig. S39**) demonstrated cytotoxic action and preference over A549 cells, with IC_{50} values of 20.20 ± 2.04 μM and 21.65 ± 1.58 μM, correspondingly. All anti-tumorigenic properties were in the range of positive control cabozantinib. Remarkably, these analogues offered comparatively low liver toxicity in comparison to the reference drugs. Furthermore, the primary SAR (structure–activity relationship) and docking investigation discovered that substitution of a nitrogen-bearing heterocycle on the group R2 (block A) may possibly enhance the c-Met kinase inhibition and anticancer action in MDA-MB-231 cells, while disarticulation by a modified benzene ring, particularly for the p-fluorophenyl or 4-fluoro- 3-methoxyphenyl moiety, on the R2 group improved cytotoxic action over A549 cells. Concurrently, these outcomes indicated that compounds **1** and **2** are potent analogues and offer a base for the advancement as new anticancer agents.

Nolan and coworkers (Nolan et al., 2020) synthesized novel promising bioactive oxazolopyrimidines *via* two main methods: annulations of the pyrimidine ring on a functionally characterized oxazole and the trimerization of benzoyl bromide in continuation to the reorganization and arrangement of the oxazolo[5,4-*d*] pyrimidine scaffold. Molecular docking analysis revealed that 7-piperazine modified three oxazolo[4,5-*d*] pyrimidines (Compounds **1**–**3**) **(Fig. S40)** might serve to be the potent VEGFR2 inhibitors acquiring high free energy of ligand–protein complex formation (ΔG: –10.1, –9.6, –9.8 kcal/mol, respectively). *In vitro* anticancer evaluations established speculative hypothesis that oxazolo[4,5-*d*] pyrimidines (Compounds **1**–**3**) including piperazine positively charged moiety and should exhibit considerably elevated cytotoxic impacts. 5-(4-Chlorophenyl)-2-phenyl-oxazolo[4,5-*d*] pyrimidin-7-yl)-

piperazin-1-ium trifluoroacetate (compound **3**) demonstrated a somewhat high anticancer action than the control doxorubicin against MDA-MB-231 cell line and possesses comparatively high-quality outcomes on OVCAR-3 and HCT-116 cells.

Sekhar et al. (2020) developed a cost-effective, facile, and effective one-pot synthesis method of thiazolo[3,2-a] pyrimidine hydrobromide analogues. α-bromination of cyclohexanone with NBS (N-Bromosuccinamide) lead to the synthesis of 2,4-diaryl-6,7,8,9-tetrahydro-4H-benzo[4,5] thiazolo[3,2-a] pyrimidine hydrobromides followed by cyclization with 3,4-d ihydropyrimidine-2(1H)-thiones, correspondingly, accompanied with PTSA (ptoluenesulfonic acid) in acetonitrile. Besides this, when cyclohexanone was substituted by alpha-tetralone and acetyl acetone gave the subsequent 9,11-diaryl-6,11-dihy dro-5H-naphtho[1′,2′:4,5]thiazolo[3,2-a]pyrimidine hydrobromide and 1-(3-methyl-5,7-diaryl-5H-thiazolo[3,2-a]pyrimidin-2-yl)ethan-1-one hydrobromide derivatives, correspondingly. The considerable characteristics of this process are that it is original, simple, cost-effective, fast, and provides good quantity. Few of the produced analogues were tested for cytotoxic action on A549, MCF-7, HeLa and SKNSH cell lines. Evaluated analogues (compounds **1**–**4**) (**Fig. S41**) exhibited the outstanding anti-proliferative potential over a range of cell lines. Especially analogue **5c** exhibited finest cytotoxicity on A549 and HeLa cells. In addition, molecular docking tests were conducted for few of the analogues (compounds **1**–**4**) on topoisomerase-II *via* Auto dock technique. Docking outcome of the compounds **2**–**4** demonstrated greater cytotoxicity in comparison to the control doxorubicin.

While searching for favorably efficient modulators capable of dealing with ABCG2-mediated MDR, Silbermann et al. (2020) synthesized and biologically tested 23 pyrimidines. Seven analogues accompanying (a) halogen- and/or nitrogen-containing residues (**Fig. S42**) acquired remarkable effectiveness over ABCG2. ABCG2-mediated Hoechst 33,342 transport was competitively inhibited by the new compounds synthesized; however, they were not the ABCG2 substrates. The major promising MDR reverser, the compound **1**, augmented SN-38-arbitrated cancer cell death at EC_{50} of 11 nM in a concentration dependent fashion, doubled SN-38 lethality in a span of 7 days at 10 nM i.e., in a time-dependent manner, while half-maximally hastened cell death in combination with SN-38 at 17 nM. No stimulation of ABCG2 was recorded. Moreover, 11 pyrimidines were discovered as triple ABCB1/ABCC1/ABCG2 inhibitors. Five acquired IC_{50} values under 10 μM countering to each transporter, categorizing them as a few of the 50 highly promising multiple target ABC transporter inhibitors. Compound **2** represents the most potent ABCB1-, ABCC1-, and ABCG2-mediated MDR reverser, indicating it to be one of the three most promising ABC transporter inhibitor and ABC transporters-arbitrated MDR reverser.

Yousif et al. (2020) studied the synthesis of new compounds opening from 2-amino-8-(2-chlorobenzylidene)-4-(2-chlorophe nyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile1 (**Fig. S43**). Reaction of diarylidene cyclohexanone with malononitrile yields compound 1. Compound **1** in turn reacts with benzoyl chloride to give compound **2**. Reaction of *N*-(8-(2-chlorobenzylidene)- 4-(2-chlorophenyl)-3-cyano-5,6,7,8-tet rahydro-4*H*-chromen-2-yl) benzamide 2 with acetic anhydride gives compound **3**. Acetic anhydride reacts with compound **1** to obtain 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-*d*] pyrimidin-4-one 4. Compound **5** is formed by the reaction of chromene derivative **1** with formic acid. Phosphorus oxychloride reacts with compounds **3**–**5** react and produce compounds **6, 7** and **8**. Reaction of chromeno[2,3-*d*] pyrimidine derivatives (compounds **6**–**8**) and hydrazine hydrate produce compounds **9**–**11**. Chromeno[2,3-*d*] pyrimidine derivatives (compounds **9** and **10**) upon reacting with glucose and xylose give compounds **11**–**14**. Finally compounds **15**–**18** are obtained by the reaction of chromeno[2,3-*d*] pyrimidine derivatives **11**–**14** with acetic anhydride. Majority of the new compounds were screened over CaCo-2, A-549 and HT-29 cancer cell lines. 2-Amino-8-(2-ch lorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8- tetrahydro-4*H*-chromene-3-carbonitrile 1 produced good cytotoxicity on HT-29 and A-549 malignant cell lines in comparison to doxorubicin as the standard drug.

Significant anti-cancer activity of 1,2,4-oxadiazole derivatives was recorded by Bommera et al. (2021) while evaluating them against malignant cell lines of human. These also exhibited anti- immunosuppressive, analgesic, inflammatory, diabetic, α, β 3-receptor antagonist, anti-helminthic, histamine-H3, antimicrobial and antiparasitic properties. A group of ten 1,2,4-oxadiazole linked 5-fluoruracil derivatives (compounds **1**–**10**) (**Fig. S44**) were produced and their structural elucidation was validated through ^{1}HNMR, ^{13}CNMR and mass spectral studies. Subsequently, these analogues were studied for their anti-proliferative action over a group of four human malignant cell lines like MCF-7, MDA MB-231, A549 and DU-145 by applying MTT assay. Among these, analogues **1**–**4** and **9** showed more potent anticancer action as compared to the standard. All the ten 1,2,4-oxadiazole linked 5-fluorouracil analogues (**1**–**10**) were tested for their anti-proliferative action over a group of four human malignant cell lines.

3.1.3. Synthetic pyrimidine derivatives acquiring anti-tumorigenic properties

Fouda et al. (2019) used easy yet effective method for the synthesis of novel collection of four pyrazole (Compounds **1**–**4**) and six pyrazolo[1,5-a]pyrimidine (Compounds **5**–**10**) analogues (**Fig. S45**) and evaluated them in-vitro for anti-tumor and antimicrobial actions. Asymmetrical and symmetrical 3,6-diarylazo-2,5,7-triaminopyrazolo[1,5-a]pyrimidine were also produced conventionally and applied microwave radiation in ultrasound environment. Human malignant cell lines, HCT-116, MCF-7, and HepG-2 were tested with the compounds under study for their anti-tumor activity in comparison to Doxorubicin as a control.

Findings of Li et al. (2019) suggested that aiming LSD1 (Histone lysine specific demethylase1) could be a potent approach for Acute myeloid leukemia (AML) therapy, the triazole- fused pyrimidine analogues are recent scaffolds for the progression of LSD1/KDM1A inhibitors. LSD1 has been documented as a significant regulator in post-translational route in epigenetics. Deregulation of LSD1 has been attributed to the cancer development. This study reported the finding of the key compound **1** and subsequent medicinal chemistry endeavors, heading towards production of compound **2** (**Fig. S46**) competitively and reversibly inhibiting LSD1 with H3K4me2, and was discerning to LSD1 over MAO-A/B. Docking analysis was conducted to rationalize the effective-

ness of compound **2**. In addition, compound **2** exhibited potent anti-proliferative action countering four leukemia cell lines (OCL-AML3, THP-1, K562 and U937) with Raji, the lymphoma cell line. Compound **2** accelerated expression of CD11b and CD86 in THP-1 cells, validating its cellular action and ability of differentiation induction.

To determine novel anticancer agents, Fatma et al. (2020) designed and synthesized a collection of substituted chromeno[2,3-d] pyrimidine and chromenotriazolo[1,5-c] pyrimidine analogues as potent anti-tumor agents. Chromeno[2,3-d] pyrimidine analogues were synthesized through the reaction between ethyl formimidate derivative 2 with diverse nitrogen nucleophiles to obtain chromenotriazolo[1,5-c] pyrimidine derivatives resulted by treating cyanomethyl derivative 14 with different electrophilic reagents. The confirmation of the chemical structures of the newly formed compounds was performed through molecular element analysis and spectral data. Entire products formed were assayed for their anti-tumor action countering two human malignant cell lines; MCF-7 (breast adenocarcinoma) and HepG-2 (hepatocellular carcinoma) plus WI-38 (normal fibroblasts). Analogues **1** and **3** exhibited considerable and preferential anti-tumorigenic action contrary to breast and liver cell lines without any harm to normal fibroblasts. The docking analysis of highly potent compounds **1, 2** and **3** (**Fig. S47**) were carried out to investigate their model of binding with protein effectors.

Lakkaniga et al. (2020) designed and synthesized varied scaffolds derived from different heterocycles and examined them as RET inhibitors. It is believed that point mutations and gene fusions of RET kinase are critical for influencing thoracic malignancies, NSCLC (non-small cell lung cancer) and thyroid cancer. Pyrrolo[2,3-d]pyrimidine derivatives were studied for RET-wt inhibition, RET V804M (drug resistant mutant) and RET gene fusion impelled cell lines. Several compounds were formed, and the SAR (structure activity relationship) studies were carried out extensively to standardize the scaffold. A bioisostere of pyrrolo[2,3-d] pyrimidine, the thieno[2,3-d]pyrimidine was also investigated for its end result on RET inhibition. A lead compound **1** (**Fig. S48**) was identified which demonstrates low nanomolar effectiveness countering to RET-wt and RET V804M. Moreover compound **1** also exhibit RET-CCDC6 driven growth retardation of LC-2/ad cells. It was also ascertained that compound **1** is a type 2 RET barrier and its potential to check tumor cells movement was also verified. Computational studies helped to propose a binding stance of compound **1** in RET compartment and enumerated the aid of specific residues for its binding. In all, compound **1** is a major lead compound which requires future assessment in biological analysis.

Sakr et al. (2020) performed a reaction of (phenylamino) but-2-enethioyl) benzamide 3 and sodium hydroxide to obtain diphenyl-4-thioxo-1,4-dihydropyrimidin-5-yl) ethan-1-one (**Fig. S49**). The reactions of compound **4** with numerous effective species such as urea, malononitrile, benzaldehyde, hydrazine, carbon disulfide and ethyl cyanoacetate were investigated. The anticancer properties of few chosen analogues were tested on two mammalian cell lines: MRC-5 cells (normal human lung fibroblast cell line) and A-549 cells (human lung cancer cell line); a few of the analogues were exceedingly potent; compound **1** exhibited the highly efficient anti-tumorigenic action.

Xie et al. (2020) reported the production of new ring-fused pyrazoloamino pyridine/pyrimidine analogues as potent FAK inhibitors and the assessment of therapeutic action on five cancer cell lines (BXPC-3, MDA-MB-231, DU145, NCI-H1975 and 786O). In general, most of the compounds exhibited strong anti-FAK enzymic potential and might efficiently inhibit some classes of cancer cell lines when compared to GSK2256098 control. Amongst them, compound **1** (**Fig. S50**) was found to be the most efficient because of high sensitivity against proliferation. Compound **1** not only inhibited FAK Y397 phosphorylation within MDA-MB-231 cell line, but also activates apoptotic cycle in a dose-dependent pattern. Moreover, computational docking studies recommended similar interaction of compound **1** and TAE-226 with FAK kinase motif.

Utilizing natural bio-friendly precursors, like glycine, glycerol, and thymine/uracil, Singh et al. (2021) reported the synthesis of pyrimidine-based cationic amphiphiles (PCAms), specifically, di-trifluoroacetic acid salts of N1-[1′-(1″,3″-diglyci natoxypropane- 2″-yl)-1′,2′,3′-triazole-4′-yl]methyl-N3-alkyl pyrimidines in decent yields. PCAms that were newly synthesized consisted of a hydrophilic head group including TFA salt of glyceryl 1,3-diglycinate and non-polar tail having C-7 and C-12N3-alkylated thymine, or uracil conjugated by means of a 4-methylene-1,2,3-triazolyl linker. The physicochemical properties of all PCAms, like significant cumulation concentration, hydrodynamic shape, diameter, and surface charge (zeta potential) were investigated. Subsequently, these PCAms were also assessed for their anti-proliferative and anti-tubercular actions on HeLa and KB-V1 cell lines and the reference strain H37Rv including MDR clinical isolate 591 of Mycobacterium tuberculosis. One PCAm respectively showed 4- to 75-times more activity in comparison to streptomycin and isoniazid, the first-line anti-tubercular drugs, countering to MDR591 (the multidrug resistant clinical isolate 591 of Mycobacterium tuberculosis).

Based on the contemplation for designing and developing anti-tumor actions of heterocyclic compound derivatives, particularly fused ring system, El-Sharkawy et al. (2021) referred to the probability of heterocyclic expansion a very significant steroidal compound utilized as a therapeutic drug. Dydrogesterone reaction with each ethylcyanoacetate and malononitrile acquiring elemental sulfur leads to the production of thiophene derivatives (compound **1** and **2**) (**Fig. S51**). In addition, reaction of dydrogesterone with a mixture of ethylcyanoacetae–urea, ethylcyanoacetate–hydrazine, or ethylcyanoacetate–thio urea produced pyrimidine derivatives (compound **3** and **4**) (**Fig. S51**) and pyrazole derivative **4**. Thienopyrimidine derivatives (**5**–**8**) (**Fig. S51**) were presented by reacting thiophene analogues (compound **1** and **2**) with benzoylisothioyanate or phenylisothiocyanate. Moreover, compounds **1** and **2** aimed at reaction with ethylcyanoacetate to generate analogues (compounds **9** and **10),** which were in turn subjected to cyclization for gaining thienopyridine analogues **11** and **12** (**Fig. S51**). Additionally, analogues **9** and **10** were directed for reaction with diverse carbonyl compounds, like cyclopentanone-elemental sulfur, salicylaldehyde, acetylacetone and malonaldehyde to obtain derivatives of coumarin **11** and **12,** fused thiophene **13** and **14,** and pyridine **15**–**18** (**Fig. S51**). Isooxazole analogues **19** and **20** (**Fig. S51**) were obtained via the reaction of hydroxylamine hydrochloride with analogues **9** and **10**. Lastly, 2-pyridone analogues **19** and **20** were produced by

the action of benzoylacetonitrile with analogues 9 and 10. Structural conformation of the compounds prepared was validated by employing ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry, while their anti-tumor property was also evaluated on the SF-268, MCF-7, NCI-H460 malignant and WI-38 normal fibroblast cell lines using Tumor cell growth assay following the method devised by the NCI (National Cancer Institute), USA (Skehan et al, 1990).

3.1.4. Synthetic pyrimidine derivatives having inhibitory actions

Diao et al. (2019) planned and produced a chain of unique pyrimidine-based benzothiazole analogues in order to target new CDK2 inhibitors as anti-cancerous agents. Preliminary biological testing revealed certain target compounds to be exhibiting *in vitro*, strong anti-tumor action over five malignant cell lines. Particularly, the derivative **(Fig. S52)** displayed effectiveness with AZD5438 with respect to four cancer cell lines comprising HeLa, PC-3, HCT116, and MDA-MB-231. Compound **1** in the present investigation proved to be extremely active acquiring potent CDK2/cyclin A2 inhibition which was almost 3-fold in comparison to AZD5438 (positive control). Molecular docking studies indicated competent binding of compound **1** with the binding site of CDK2. Subsequent studies suggested the ability of compound **1** to accelerate cell cycle check with apoptosis in a concentration- dependent manner. These interpretations recommend pyrimidine-benzothiazole hybrids to signify a novel grade of CDK2 inhibitors and conduct further studies targeting to produce promising anticancer agents.

COX-2 (Cyclooxygenase-2) inhibition and free radicals (scavenging) are crucial objects in cancer therapy. Therefore, Omar et al. (2019) synthesized in lab, triazolopyrimidines and sulfanylpyrimidines with subsequent evaluation as antioxidant and anticancer COX-1/2 inhibitors. Synthesized compound **1** (**Fig. S53**) exhibited similar growth inhibitor activities as 5-fluorouracil over MCF-7. Compound **2** (**Fig. S53**) demonstrated wide range anticancer action countering four tested cancer cell lines. Analogues **3**–**7** turned out to be more potent antioxidants as compared to trolox. Also established by docking studies, analogues **4**–**7** showed elevated COX-2 inhibition and selection. According to the results, analogue 6f could be regarded as a potential antioxidant and anticancer lead molecule exhibiting COX-2 inhibition which needs subsequent derivatization and analysis.

Rahim et al. (2019) synthesized indole/isatin conjugated phenyl-amino-pyrimidine derivatives to characterize and evaluate their ability *in vitro* as BCR-ABL inhibitors. Amid the collection, all15 compounds showed more cytotoxic activity with respect to the standard Imatinib over the K-562 cell line. Compound **1** (**Fig. S54**) was the most potent amid all other derivatives with approximately two times more efficacy than the control imitanib. *In vitro* enzymatic investigations with ABL kinase recombinant enzyme potent inhibitory action in for majority of these newly synthesized analogues. Additionally, computational studies including modelling were performed to demonstrate interaction of BCR-ABL proteins with the molecules under investigation.

Asati et al. (2020) in their work performed 3D-QSAR, pharmacophore modeling and docking on pyrazolo-pyrimidine derivatives for identification of the vital characteristics needed for the expansion of potent PIM kinase barriers. The PIM kinases belong to serine/threonine kinase family related to the CAMK (Ca^{2+}/calmodulin-dependent protein kinase) group. Development of various cancer types may be attributed to the anomaly of PIM kinase pathway. The phase expounded pharmacophore (ADRR_1) hypothesis comprise of indispensable characteristics like, one hydrogen bond donor, one hydrogen bond acceptor, and two aromatic rings, necessary for the action. The 3D-QSAR investigation was carried out by means of field-based and atom-based methods generating elevated regression coefficients for the test (Q2 = 0.71; 0.69) and training (r^2 = 0.87; 0.96) sets, successively. The docking analysis exhibited fine binding interactions with GLU12, LYS67, GLU171 and ASP128 essential amino acids. The virtual selection analysis was conducted via ZINC database using ADRR_1 pharmacophore, capable of producing 7006 molecules like drugs. Different docking approaches were applied further to screen four target compounds *viz*., ZINC12941871, ZINC59456489, ZINC59456449, and ZINC59456444. The compound ZINC59456449 demonstrated finest docking position (comparable to crystal ligand) with docking scores, SP (-7.94 kcal/mol) and XP (-8.42 kcal/mol). The ADME and MMGBSA factors exhibited the exceptional scores that could be accounted for the standardization of active compounds. These findings in future may prove to be of great help for the scientists in developing of novel substitutes against PIM-1 kinase.

3.2. Biological targets of pyrimidine derivatives

Pyrimidines have also been shown to have anticancer properties by inhibiting a variety of targets including the tyrosine kinase of the Epidermal Growth Factor Receptor (EGFR), Janus Kinase (JAK), Mitotic Checkpoint Protein Kinase (Mps1), carbonic anhydrase, and MDM-2 (Kilic-Kurt et al., 2018). They have a high selectivity for CDK9 over other CDKs and can activate caspase 3, decrease Mcl-1 anti-apoptotic protein levels, and induce cancer cell death (Shao et al., 2013).

4. Conclusion

As evident from the recent advances listed in this review pyridine and pyrimidine analogues are providing appealing opportunities for cancer therapy. The hetrocyclic nitrogen containing rings of pyridine and pyrimidine are extensively exploited in drug research and development because of their coordination power and function in various biological activities. In addition to wide latitude offered in chemical modification, the pyridine and pyrimidine analogues have demonstrated biological activity against wide range of cancer targets. The mechanism of anticancer activity varies from cell cycle arrest, cytotoxicity, and apoptosis to ROS generation. As an initiation step, plan of imitating natural sources was made applicable to develop pyridine/pyrimidine analogs expressing antineoplastic activities by challenging the natural source binding with targeted enzyme(s) or receptor(s). The approach of exchange with different rings and moieties on the central configuration was executed to get an assortment of pyridine/pyrimidine analogues as well as complexes of pyridine/pyrimidine. Considering the polypharmacological trend, the coupling of pyridine/pyrimidine basic configurations with accessible bioactive was carried out for developing new unique compounds with manifold chemotherapeutic uses. Initially, pyrimidine/pyridine-origin metal composites were created as antiproliferative agents however; the recent advances highlight that minor

molecule like pyridine and pyrimidine provide potent opportunity for progression of anticancer drug development countering multiple targets.

5. Future prospects

The research till date has unveiled numerous pyridine and pyrimidine derivatives as promising anti-neoplastic agents. Digging deeper into the rooted data, several more novel compounds acquiring anti-proliferative and/or allied biological potential could be accomplished in varied aspects. Importantly, logical designing and production of new bioactive could be achieved *via in silico* methods, structural variation, and molecular fusion of core bioactive compound's backbone. Anticipation of adding new molecules would require further studies for biological activity evaluations of engineered pyridines and pyrimidines for different type of cancers whose cure is difficult in cancer therapeutics. The biological action of these two heterocycles will aid the researchers to strategize, classify and execute new methods for discovering novel anticancer drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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