PIM KINASES INHIBITORS AND PYRIMIDINE-BASED ANTICANCER AGENTS

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Abstract

Human phosphatidyl inositol mannoside kinases (Pim kinases) are important biological target for discovery of new anticancer agents. In addition, Pyrimidines have a good contribution as building blocks of many anticancer agents. Hence, a literature survey about Pim kinases inhibitors and pyrimidine-based anticancer agents have been achieved. In this survey, we introduced Pim kinase inhibitors under clinical assessment including imidazo[1,2-*b*]pyridazines, isatins, thiazolidine-2,4-diones, pyridinamines, and diaminopyrazoles. In addition, Pim kinase inhibitors under development were presented. These compounds include pyridine-quinolines, benzimidazoles indoles, cyano pyridines, pyridothieno[3,2-*d*]pyrimidin-4-ones, oxadiazole, and 3,4-dihydropyrrolo[1,2-a]pyrazin-1(2*H*)-ones. Furthermore, different pyrimidine-based anticancer agents have been discussed.

Keywords: Pim kinases inhibitors; Pyrimidine; Anti-cancer agents

1. Introduction

Cancer is a disease in which some of the body cells grow uncontrollably and spread to other parts of the body. It can start anywhere in the body and can be cancerous or not (benign). It can spread into, or invade, nearby tissues and travel to distant places in the body to form new tumors. Cancer cells differ from normal cells in many ways, such as growing in the absence of signals, ignoring programmed cell death, invading nearby areas, and hiding from the immune system. They also accumulate multiple changes in their chromosomes, rely on different kinds of nutrients, and make energy from nutrients in a different way than normal cells. Researchers have developed therapies to target these abnormal features of cancer cells, such as preventing blood vessels from nurturing the tumors and starving the tumor of needed nutrients (N.C. Institute 2021).

Cancer is caused by changes to genes that control how cells grow and divide. Each person's cancer has a unique combination of genetic changes, and even within the same tumor, different cells may have different genetic changes. Metastatic cancer is cancer that has spread from the place where it first formed to another place in the body. It has the same name and type of cancer cells as the original but can cause severe damage to how the body functions (Zhang *et al.* 2014).

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Breast cancer (2.26 million cases), lung cancer (2.21 million cases), colon and rectal cancer (1.93 million cases), prostate cancer (1.41 million cases), non-melanoma skin cancer (1.20 million cases), and stomach cancer (1.20 million cases) were the most prevalent types of cancer in 2020. Lung cancer caused 1.80 million fatalities in 2020, followed by colon and rectum cancer (916 000 deaths), liver cancer (830 000 deaths), stomach cancer (769 000 deaths), and breast cancer (685 000 deaths). Every year, 400 000 children are diagnosed with cancer. The most prevalent malignancies differ between nations. In 23 nations, cervical cancer is the most prevalent type (WHO: 2022).

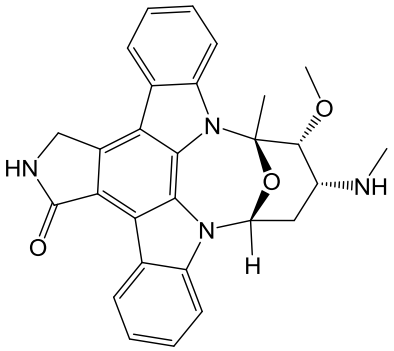
2. Pim kinase receptor

Human phosphatidyl inositol mannoside kinases (Pim kinases) are a family of serine/threonine kinases composed of three members; Pim-1, Pim-2 and Pim-3 (Zhang *et al.* 2018) known as human proviral integration moloney (Pim) kinases. PIM-1 kinase is directly involved in the development of tumors in a number of hematological malignancies, including leukemia and lymphoma. Moreover, Pim-1 and Pim-2 are overexpressed in hematological and solid tumors (Zhang *et al.* 2018), whereas Pim-3 is overexpressed in hepatocellular, pancreatic, and colon carcinomas (Mukaida *et al.* 2011). PIM-1 kinase is overexpressed in a number of solid malignancies, including breast, colon, prostate, and hepatic cancers. Moreover, it has a role in a variety of biological processes, including drug resistance, cell proliferation, and apoptosis (Rathi *et al.* 2021). The Pim-1 is considered as a very attractive target for pharmacological inhibition in cancer therapy (Swellmeen *et al.* 2017).

The Pan-Pim kinase domain is characterized by the unique presence of a proline amino acid residue with a tertiary amine in the hinge region, which is not found in other protein kinases. This structural feature enabled the design of selective pan-Pim kinase inhibitors devoid of off-target activity on other kinases (Alnabulsi *et al.* 2020).

2.3.Classification of Pim

Pan-Pim kinase inhibitors are classified (depending on their interactions with hinge residues) into two broad types: ATP-mimetic and ATP-competitive inhibitors. ATP-mimetics (staurosporine (**1)** and LY333531 (**2))** form one canonical hydrogen bond (HB) with the backbone CO of the hinge region. By contrast, ATP-competitive inhibitors (SMI-4a (**3)** and LY294002 (**4))** compensate for the lack of forming canonical HBs with the hinge region by forming other polar contacts inside the ATP-binding site (Xia *et al.* 2009, Lin *et al.* 2010, Liang *et al.* 2014).



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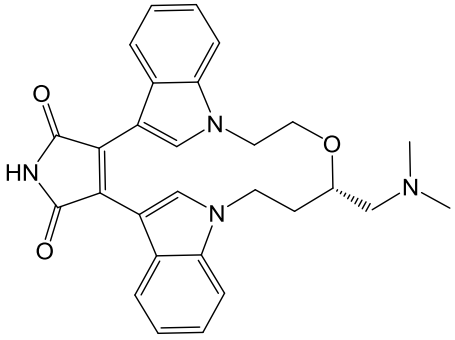

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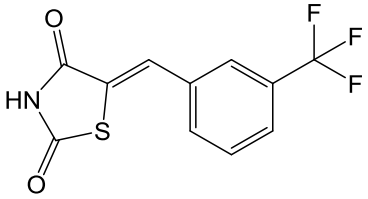

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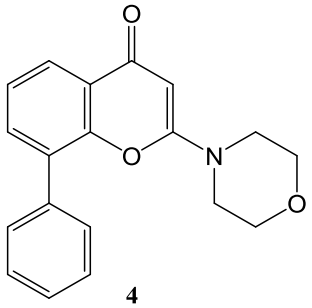

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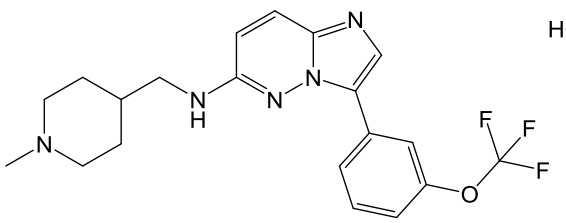
2.4.Pim kinase inhibitors under clinical assessment

a) Imidazo[1,2-*b*]pyridazines

SGI-1776 (**5**) was the first Pim inhibitor clinically evaluated in patients with relapsed and/or refractory leukemias. A selective Pim-1 inhibitor TP-3654 (**6**) is undergoing clinical assessment in patients with advanced solid tumors (Alnabulsi *et al.* 2020).



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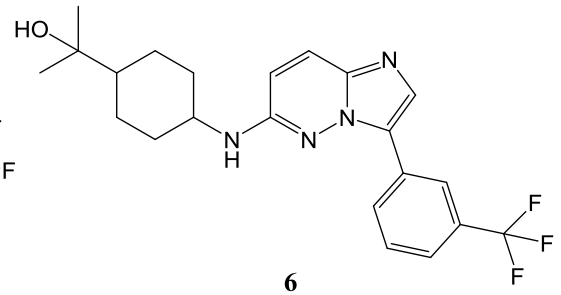

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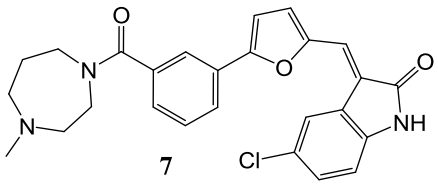
Isatin derivatives

CX-6258 **(7), a**n isatin derivative, was identified as a potent pan-Pim inhibitor with cellular anti-proliferative activity against different types of cancer cell lines. it is undergoing clinical evaluation (Asati *et al.* 2019).



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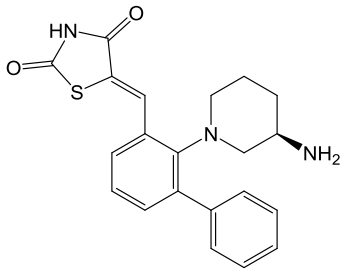
b) Thiazolidine-2,4-dione derivatives

The thiazolidine-2,4-dione derivative, AZD1208 **(8),** was identified as potent and selective Pim inhibitor with potential anticancer activity. This compound was investigated preclinically, followed by clinical assessment in patients with solid and hematological tumors (Keeton *et al.* 2014, Cortes *et al.* 2018).



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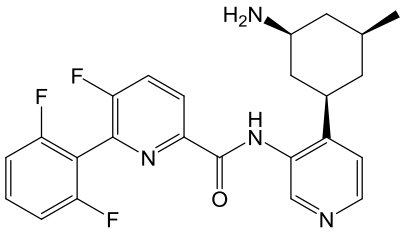
c) Pyridinamine derivatives

The clinical candidates PIM447 **(9)**, LGB321 **(10)**, and NCB053914 **(11)** showed promising activity against different types of Pim kinases. PIM447 is currently in Phase I

clinical studies in patients with relapsed and/or refractory multiple myeloma (Raab *et al.* 2019). Likewise, preclinical studies showed that INCB053914 can be of benefit as a chemotherapy against hematological malignancies if it is used alone or in combination with other anticancer agents (Koblish *et al.* 2018).



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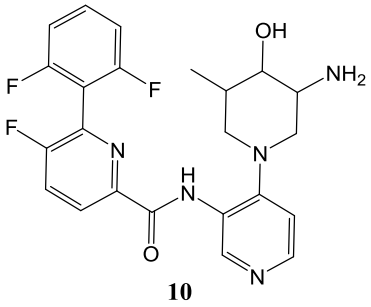

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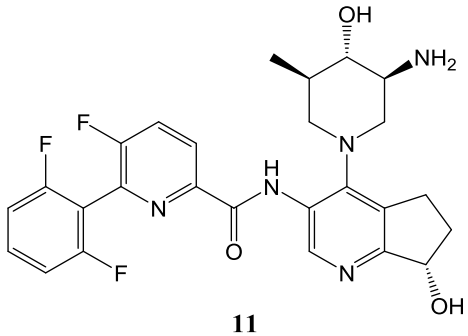

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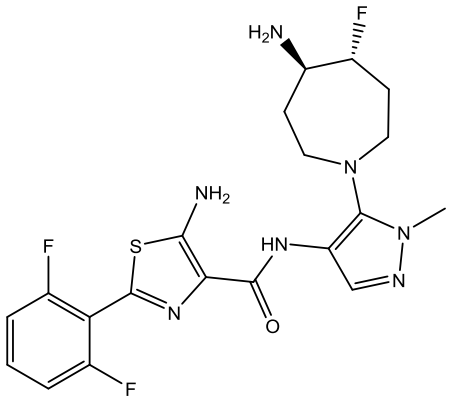
d) Diaminopyrazole

GDC-0339 (**12**), a diaminopyrazole derivative, was identified as a novel, selective, oral Pim kinase inhibitor. It was investigated clinically as potential anticancer agent that could be further investigated for use against multiple myeloma (Burger *et al.* 2013).



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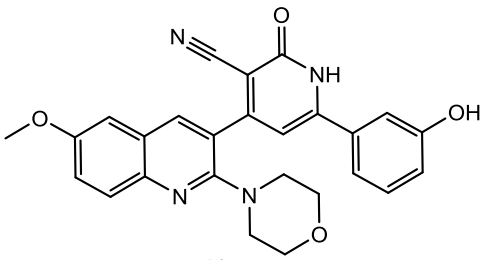
2.5.Pim kinase inhibitors under development

a) Pyridine-quinoline derivative

In 2023, El-Miligy *et al.* synthesized new quinoline-pyridine hybrids as Pim kinas inhibitors. Compounds **(13),** (**14), (15),** and (**16)** showed potent *in-vitro* PIM-1 kinase inhibitory activity. While, (**14)** showed potent *in-vitro* PIM-2 kinase inhibitory activity. Kinetic studies using Lineweaver–Burk double-reciprocal plot indicated that the tested compounds behaved as competitive inhibitors (El-Miligy *et al.* 2023).



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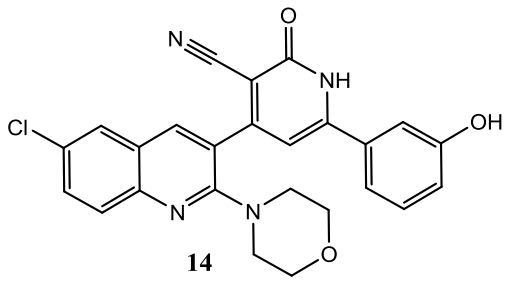

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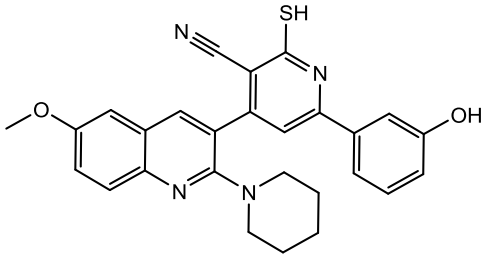

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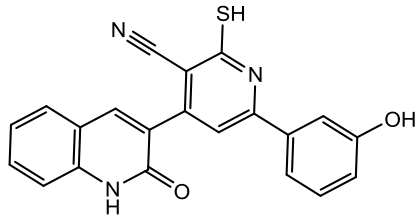

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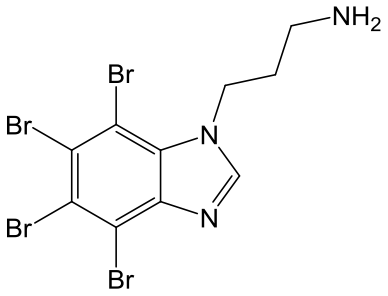
b) Benzimidazole derivatives

In 2018, Chojnacki *et al*. were synthesized a new series of 1*H*-benzimidazole derivatives as PIM1 kinases inhibitors. PIM1 kinase inhibition was assessed. All derivatives inhibited the activity of PIM1 kinase. Compounds (**17)** and (**18)** were the most efficient members (Chojnacki *et al.* 2018).



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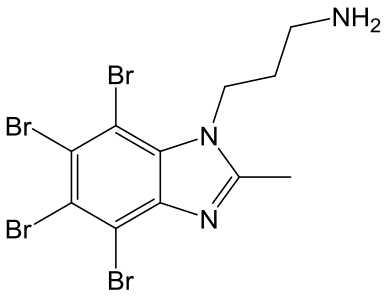

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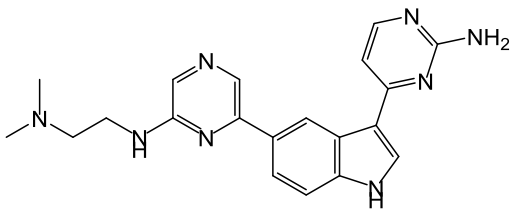
c) Indole derivatives

In 2018, a potent Pim kinase inhibitor (**19)**, derived from meridianin C, was optimized by the replacement of 2-aminopyrimidine with substituted benzene. The optimization of the C-3 and C-5 positions of indole yielded compound (**20)** with improved cellular potency and high selectivity against a panel of 14 different kinases (More *et al.* 2018).



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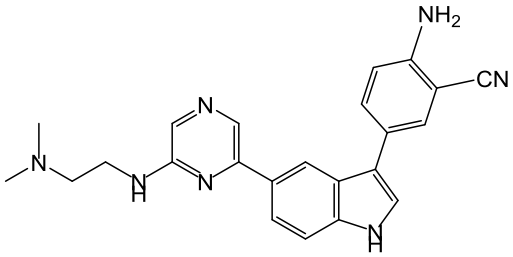

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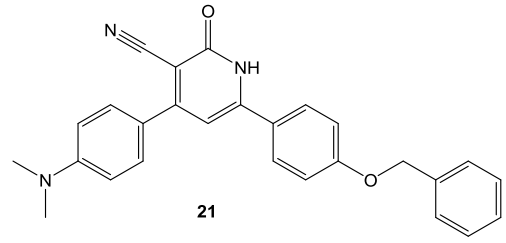
d) Cyano pyridine derivatives

In 2022, Mona *et al.* synthesized a new series of 3-cyanopyridines as PIM-1 kinase inhibitors. Anti-tumor activity was assessed against PC-3 and DU-145 prostate cancer cell lines. The most powerful derivatives (**21)**, (**22)**, (**23)**, and (**24)**, were chosen for further examination of their inhibitory potential on both kinases (PIM-2 and PIM-3). Upon loading compound (**22)** in a cubosomes formulation with nanometric size, improvements in cytotoxicity and inhibitory effect on PIM-1 kinase were observed (Ibrahim *et al.* 2022).



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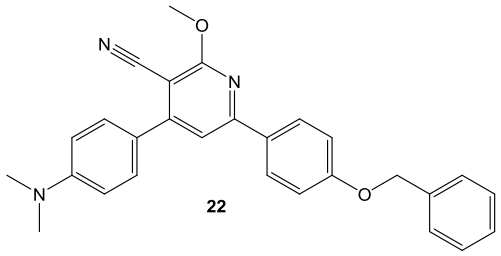

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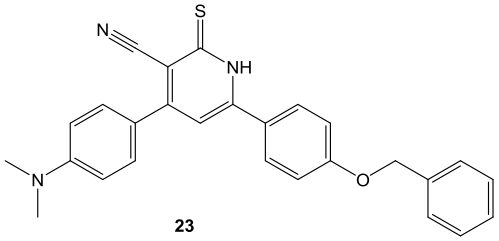

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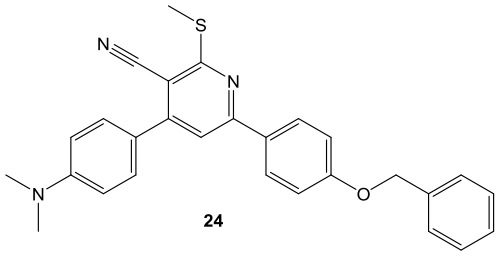

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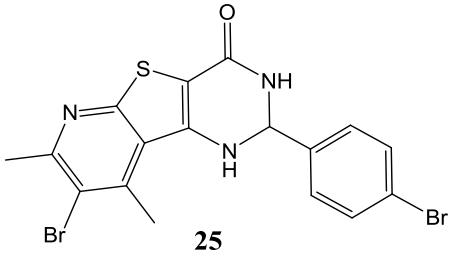
e) Pyridothieno[3,2-*d*]pyrimidin-4-one derivatives

In 2018, El-Nassan *et al*. prepared three series of 2-arylpyridothieno[3,2-*d*]pyrimidin-4-ones , pyridothienotriazolopyrimidines and 4-imino-pyridothieno [3,2-*d*]pyrimidines to improve the pim-1 inhibitory activity of the previously reported 2-arylpyridothieno[3,2-*d*]pyrimidin-4-ones. All the test compounds showed highly potent pim-1 inhibition with IC_{50} in the range of 0.06–1.76 µM. Compounds (**25), (26), (27),** and **(28)** were the most active members (El-Nassan *et al.* 2018).



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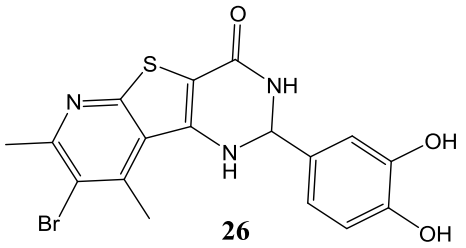

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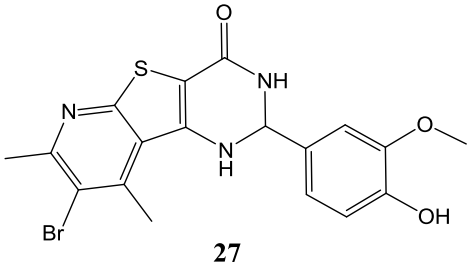

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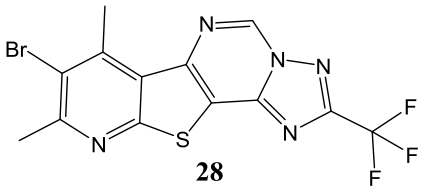

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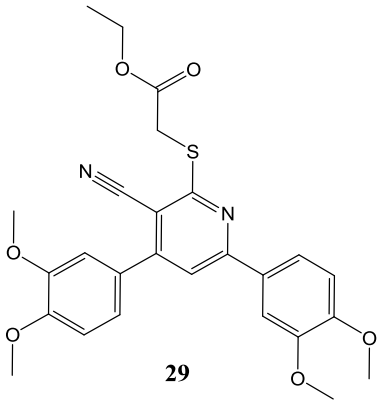
In 2019, a new series of pyridine and thieno[2,3-*b*]pyridine derivatives were synthesized and screened *via* MTT assay for cytotoxic activities against normal fibroblasts and four cancer cell lines (HepG-2, Caco-2, MCF-7 and PC-3) by Rizk *et al* (Rizk *et al.* 2019).

Compounds (**29), (30)**, (**31)** and (**32)** exhibited anticancer activities at nanomolar IC_{50} with promising safety. Furthermore, they exerted promising dual VEGFR-2/PIM-1 kinase inhibition.



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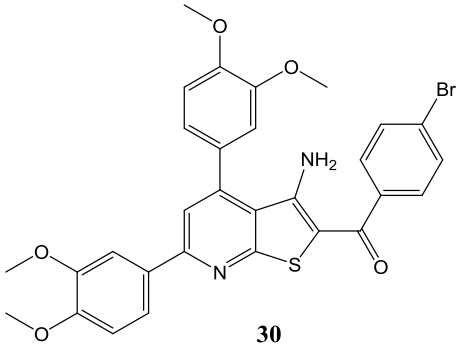

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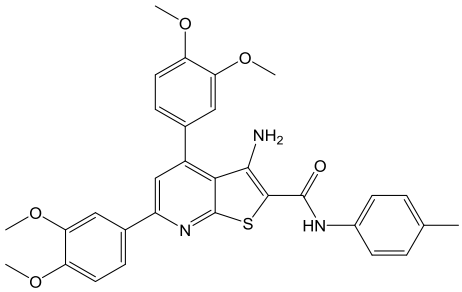

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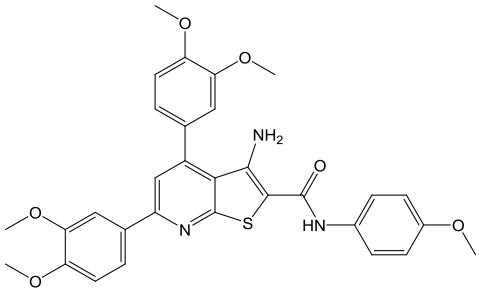

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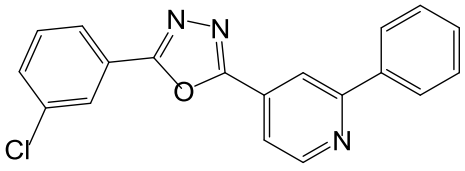
Oxadiazole derivatives

In 2023, Castanet et al. designed and synthesized a new PIM-1 kinase targeting 2,5-disubstituted-1,3,4-oxadiazoles as potential anti-cancer agents. In vitro cytotoxicity experiments have disclosed (**33)** as the most potent derivative against PC-3 cells (IC_{50} = 16 nM) compared to the reference drug Staurosporine (IC_{50} = 0.36 μM), also eliciting good cytotoxicity against HepG2 and MCF-7 cells (IC_{50} = 0.13 and 5.37 μM, respectively).



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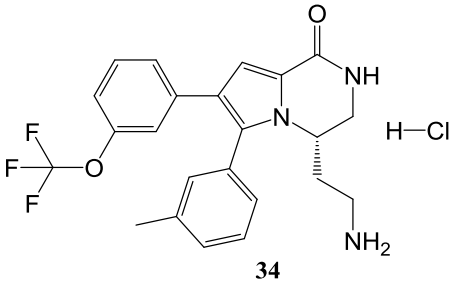
f) 3,4-Dihydropyrrolo[1,2-a]pyrazin-1(2H)-one derivatives

In 2022, Casuscelli *et al.* described a structure-based scaffold decoration and a stereoselective approach to discover new PIM kinases inhibitors. The synthesis, structure–

activity relationship studies, chiral analysis, and pharmacokinetic data of 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one derivatives revealed that compound (**34)** is an excellent Pim1 and Pim2 inhibitor (Casuscelli *et al.* 2022).



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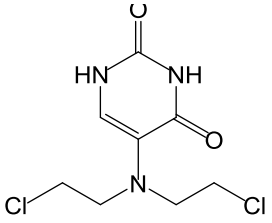
3. Pyrimidine derivatives as versatile anti-cancer molecules

Pyrimidines are nitrogen-containing hetero cycles (Mahapatra *et al.* 2021) known for anticancer (N *et al.* 2021), Pyrimidines have many properties in common with pyridine, such as reduced resonance stabilization and difficulty in *N*-alkylation and *N*-oxidation The structures of well-known, commercially available medications including Uramustine (**35)**, Tegafur **(36)**, Floxuridine **(37)**, and Cytarabine (**38)** among others, had these similar characteristics (Selvam *et al.* 2015).



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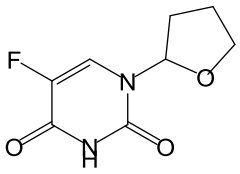

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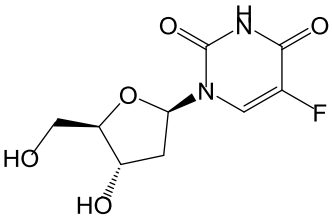

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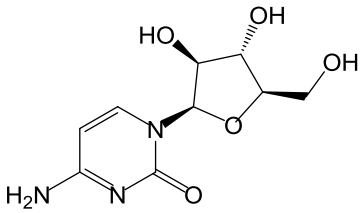

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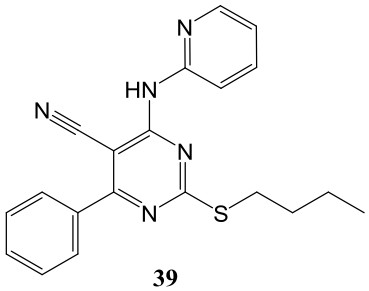
3.1.Pyrimidines as EGFR inhibitors

In 2020, Eissa *et al.* designed and synthesized a series of pyrimidine-5-carbonitrile derivatives as *ATP* mimicking tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR). Compound (**39)** showed 4.5- to 8.4-fold of erlotinib activity against HCT-116, HepG-2, MCF-7, and A549 cells with IC_{50} values of 3.37, 3.04, 4.14, and 2.4 µM respectively. Moreover, compound (**39)** was the most active compound against both

$EGFR^{WT}$ and $EGFR^{T790M}$, exhibiting IC_{50} values of 0.09 and 4.03 µM, respectively (Nasser *et al.* 2020).



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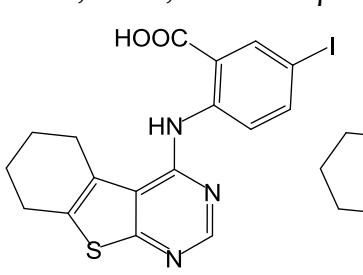
In 2019, Elmetwally *et al*. designed and synthesized a series of thieno[2,3-*d*]pyrimidine derivatives as an EGFR and HER2 tyrosine kinase inhibitors. Compounds (**40), (41),** and **(42)** showed promising inhibitory activities against $EGFR^{WT}$ with IC_{50} values 0.174, 0.630, and 1.440µM, respectively (Elmetwally *et al.* 2019).



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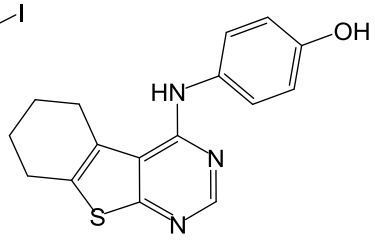

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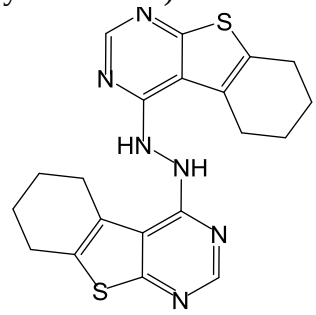
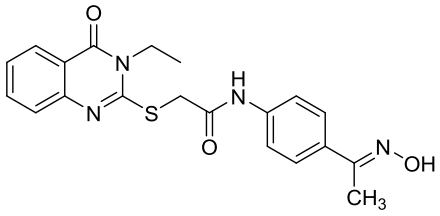


42

3.2.**Pyrimidines as VEGFR inhibitors**

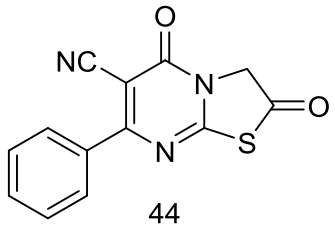
In 2020, Mahdy *et al*. designed and synthesized as new series of quinazoline-based derivatives having the structural features of VEGFR-2 inhibitors. Anti-proliferative activities were evaluated against three human cancer cell lines (HepG-2, MCF-7 and HCT-116) using MTT assay method. Compound (**43)** showed high activity against VEGFR-2 with an IC_{50} value of 2.5 ± 0.04 µM, compared to that of sorafenib (IC_{50} = 2.4 ± 0.05µM) (Mahdy *et al.* 2020).



43

3.3.Thymidylate synthase (TS) inhibitors

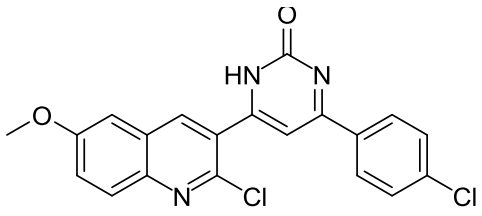
In 2017, a new series of pyrimidine derivatives were designed and synthesized as Thymidylate synthase (TS) inhibitors. Compound (**44)** showed promising TS inhibitory activity (El-Naggar *et al.* 2017).



44

3.4.Tubulin polymerization inhibitors

In 2021, a new series of pyrimidine derivatives have been designed and synthesized to possess the same essential pharmacophoric features of colchicine binding site inhibitors. The synthesized compounds were tested *in vitro* against a panel of three human cancer cell lines (HepG-2, HCT-116, and MCF-7) using colchicine as a positive control. Compound (**45)** exhibited the highest tubulin polymerization inhibitory effect with IC_{50} value of 10.5 nM (Hagras *et al.* 2021).



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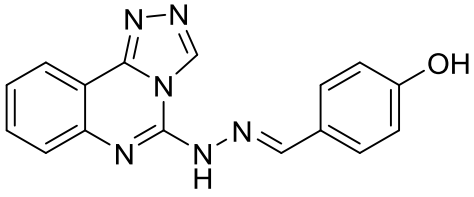
3.5.**DNA intercalators and topoisomerase II inhibitors**

In 2020, A new series of 1,2,4-triazolo[4,3-*c*]quinazoline derivatives was designed and synthesized as Topo II inhibitors and DNA intercalators. The cytotoxic effect of the new members was evaluated *in vitro* against a group of cancer cell lines including HCT-116, HepG-2, and MCF-7. Compound (**46)** exhibited promising anti-proliferative activities with potential inhibition for topoisomerase II. Molecular docking studies against crystal structure of DNA-Topo II complex revealed that compound has good binding pattern (Alesawy *et al.* 2021).



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مثبطات كينازات بيم وعوامل مضادة للسرطان قائمة على نواة الببيريميدين.

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بريد إلكتروني للباحث الرئيسي : Ibrahimeissa@azhar.edu.eg

تعتبر كينازات مانوسيد فوسفاتيديل إينوزيتول البشرية (كينازات بيم) هدفًا بيولوجيًا مهمًا لاكتشاف عوامل جديدة مضادة للسرطان، بالإضافة إلى ذلك فإن نواة البيريميدين لها مساهمة جيدة باعتبارها لبنات بناء للعديد من العوامل المضادة للسرطان،ومن ثم تم إجراء مطالعة مرجعية حول مثبطات كينازات بيم والعوامل المضادة للسرطان القائمة على نواة البيريميدين . في هذا الاستطلاع قدمنا نبذة عن أمراض السرطان وطرق علاجها ودوافع اعتماد العلاج المضاد للسرطان علي مثبطات كينازات بيم. وقد استعرض البحث نماذج من مثبطات بيم كيناز تحت التقييم السريري يشمل نماذج لمركبات تحتوي علي أنوية ، ايميدازول(1 ،2- ب) بيريدازين ، إيزاتين ، ثيازوليدين -٢،٤ ديون ، بيريدينامين ، وديااامينوبيرازول. بالإضافة إلى ذلك تم تقديم مثبطات كينازات بيم قيد التطوير تشمل علي نواة بيريدين،كينولين ، وإندول بنزيميدازول ، وسيانو بيريدين ، وبيريدوثينو [٣،٢-د] بيريميدين-٤-منها ، وأوكساديازول ، و ٣،٤-ديهيدروبيرولو [١،٢-أ] بيرازين -١ (H -ones٢) ،علاوة على ذلك تمت مناقشة مركبات متنوعة مضادة للسرطان تعتمد على البيريميدين كنواة أساسية في بنائها.

الكلمات المفتاحية: مثبطات بيم كينازات. بيريميدين. عوامل مضادة للسرطان