AN INSIGHT INTO MEDICINAL PROPERTIES OF QUINOXALINE SCAFFOLD, WITH A FOCUS ON THEIR ANTICANCER POTENTIAL AS INTERCALATING AGENTS

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ABSTRACT

The antitumor properties of synthetic heterocyclic compounds are among the most important properties that can be made use in medicinal chemistry. More specifically, their significant cytotoxic effects against many types of human tumor cells, as well as their roles as various topoisomerase inhibitors. In recent years، quinoxaline derivatives have frequently attracted the interest of medicinal chemistry researchers due to their promising anticancer properties. The present study is a review of the latest advances in quinoxaline derivative-related research, with a focus on their anticancer activities as DNA intercalator.

Keywords

Anticancer, quinoxaline, DNA intercalator, topoisomerase.

1. Introduction:

Cancer is one of the most serious diseases, it is characterized by rapid, uncontrolled growth of cells and abnormal cell division with increased rate of DNA synthesis and very fast metabolism (Bertram, 2000). This uncontrollable growth can spread to distant sites of the different body organs resulting in formation of a lump called a tumor, however, this is true of all cancers except leukemia (cancer of the blood that results in high number of abnormal white blood cells). In 2022 there were an estimated twenty million new cancer cases and 9.7 million deaths. There are more than 100 cancer types, each requiring unique diagnosis and treatment (Lone *et al.*, 2022).

1.1. Difference between cancer and normal cells.

Cancer cells differ from normal cells by the following hallmark traits *(Wang et al.*, 2023):
(a) Ability to proliferate due to self-sufficiency in growth signals.
(b) Insensitivity to growth inhibitory signals.
(c) Evasion of apoptosis and senescence.
(d) Limitless replication potential.
(e) Sustained angiogenesis.
(f) Potential to invade tissue and metastasize.

1.2. Causes of cancer (etiology)

Certain genes control the life cycle, the growth, function, division, and death of a cell; When these genes are damaged, the balance between normal cell growth and death is disrupted. This resulted in the initiation of cancer (Reynolds & Schecker, 1995).

The following is a partial list of factors known to damage DNA and increase the risk of cancer:

1.2.1 Mutation

Every day, some genes are damaged, and cells are quite adept at fixing them. However, as damage accumulates over time, cells are less likely to be able to repair the damaged genes (Gitter, 2001).

1.2.2. Environment

Environmental exposure to ultraviolet sunlight radiation has been linked to the development of cancer. Pollutants in the air, such as smoke, dust, asbestos, and arsenic, can potentially cause cancer (Siemiatycki *et al.*, 2004).

1.2.3. Microbes

Viruses have been linked to at least six human cancers and are responsible for 15% of all cancer deaths worldwide. Burkitt's lymphoma and nasopharyngeal cancer, for example, are caused by the Epstein-Barr virus. Human papillomaviruses are sexually

transmitted viruses that can cause cervical cancer. HIV can cause Kaposi's sarcoma and lymphoma, while hepatitis B can cause 80% of all liver malignancies (Patrick, 2013).

1.3. Treatment of cancer

Specific approaches to treat cancer depend upon the specific type, location and age of cancer. There are several fundamental techniques available to treat cancer including surgery, radiation, immunologic treatment and chemotherapy. Generally, a combination of these methods are used (Rosenwald *et al*., 2002).

1.3.1. Surgery

This method of treatment is used for treatment of non-hematological, non-metastasized and relatively small size tumors as mastectomy and prostatectomy (Ko, 2009).

1.3.2. Radiation and photo radiation therapy

Radiation therapy works by damaging cancer cells DNA. It takes place directly via ionization of the atoms which make up the DNA chain, or indirectly via ionization of water molecules, forming free hydroxyl radicals which then damages DNA (Yu *et al*., 2022). Radiotherapy is used for treatment of almost every type of either benign or malignant tumors (Yu *et al*., 2022).

1.3.3. Immunological therapy

The main goal of this method of treatment is stimulation of the immune system to eradicate malignant cancer cells that are responsible for the disease. This can be either through immunization of the patient, or through the administration of therapeutic antibodies (Waldmann, 2003).

1.3.4. Chemotherapy

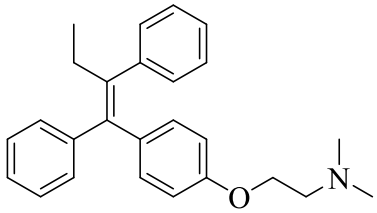
Cancer chemotherapeutic agents are used as monotherapy or as a complementary treatment to either surgery or radiation therapy. They are effective against metastasized tumors or residual tumors after surgery or radiotherapy. Most traditional anticancer drugs work by disrupting the DNA function (cytotoxicity) (Liu, 1989). Some of them act on DNA directly as DNA intercalators (e.g. doxorubicin) (Liu, 1989).

2. Brief list of some chemotherapy:

2.1. Hormone-based therapies.

Anti-hormonal compounds are administered to prevent the unwanted hormone from binding to its receptor. Tamoxifen **1**, selective estrogen receptor modulators (SERMs) (Bond, 2007), is used in treatment of breast cancer. Flutamide **2**, oral non-steroidal anti-androgen، blocks the binding of testosterone and its active metabolite

dihydrotestosterone (DHT) to androgen receptor, is used for treatment of prostate cancer (Taplin & Ho, 2001).



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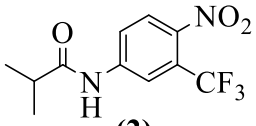

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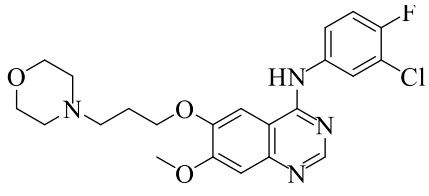
2.2. Protein kinases inhibitors

Protein kinases (PKs) catalyze phosphorylation of different cellular substrates. Phosphorylation in turn regulates various cellular functions. Under pathological conditions, PKs can be deregulated, leading to alterations in the phosphorylation, resulting in uncontrolled cell division, apoptosis inhibition and consequently tumor (Shchemelinin, Sefc, & Necas, 2006).

Gefitinib **3** (Mitsudomi *et al*., 2010; Mok *et al*., 2009), erlotinib **4** (Rosell *et al*., 2012) and icotinib **5** (Y. Shi *et al*., 2013; Y. K. Shi *et al*., 2017) are an anilinoquinoxaline-derived first-generation EGFR TKIs that reversibly bind to the kinase domain of EGFR and potently inhibit the receptor when it has been constitutively activated by common mutations. These drugs are used for treatment of non-small cell lung cancers (NSCLCs)



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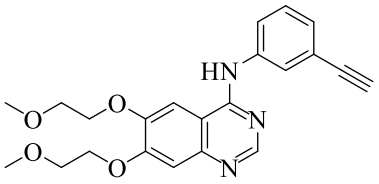

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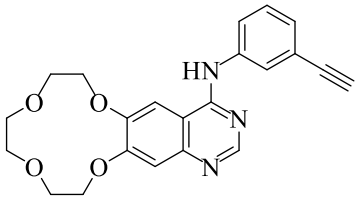

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2.3. DNA as a molecular target for anticancer agents

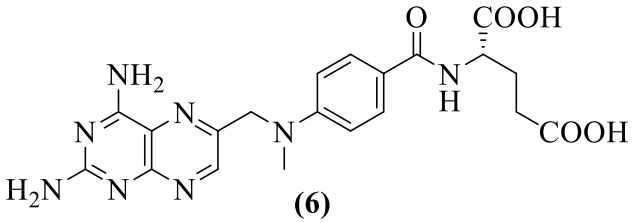
A large percentage of chemotherapeutic anticancer agents interfere with DNA biosynthesis, directly interact with DNA or prevent the proper DNA relaxation (through the inhibition of topoisomerases) (Palchaudhuri & Hergenrother, 2007). DNA small molecule interactions are driven by two main modes of binding: covalent and non-covalent (Kumar, Xue, & Arya, 2011).

2.3.1. Drugs that interfere with DNA biosynthesis (Antimetabolites)

Antimetabolites are compounds that prevent the biosynthesis of normal cellular metabolites due to a close chemical structural similarity between the natural metabolite and the anti-metabolite (Peters *et al.,* 2000).

2.3.1.1. Dihydrofolate reductase inhibitors

Dihydrofolate reductase (DHFR) functions as a catalyst for reduction of dihydrofolate to tetrahydrofolate, which generates reduced folate carriers of one carbon fragments, and it is an important co-factor in biosynthesis of nucleic acids and amino acids. Inhibition of DHFR leads to partial depletion of intracellular reduced folates with subsequent limitation of cell growth (Roth, 1986). Methotrexate **(**MTX) **6** is a potent inhibitor of DHFR (Jolivet, Cowan, Curt, Clendeninn, & Chabner, 1983).



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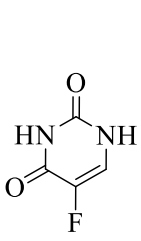
2.3.1.2. Thymidylate synthase inhibitors

Thymidylate synthase (TS) is essential for production of deoxythymidine triphosphate (dTTP) which is involved in DNA synthesis. 5-Fluorouracil (5-FU) **7** and raltitrexed **8**, pyrimidine analogs, inhibit the TS in the folate synthesis pathway (Adjei, 2000).



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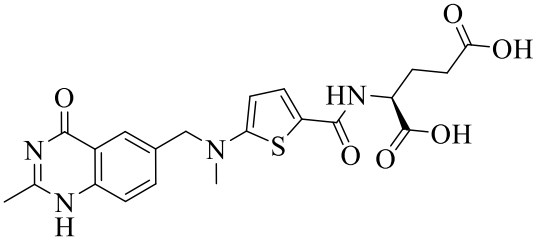

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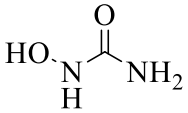
2.3.1.3. Ribonucleotide reductase inhibitors

Ribonucleotide reductase is responsible for the conversion of ribonucleotide diphosphates to deoxyribonucleotide diphosphates. Ribonucleotide reductase is inhibited directly by hydroxycarbamide (hydroxyurea) **9**.



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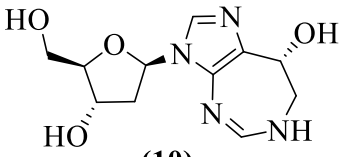
2.3.1.4. Adenosine deaminase inhibitors

Adenosine deaminase catalyzes the deamination of adenosine to inosine. Inhibition of such enzyme leads to a build-up of dATP in the cell, which, in turn, inhibits ribonucleotide reductase. The anti-leukaemic drug, pentostatin **10** is a powerful inhibitor of adenosine deaminase (Patrick, 2013).



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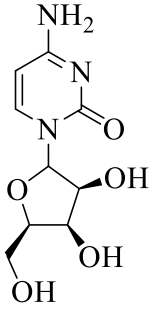
2.3.1.5. DNA polymerases inhibitors

DNA polymerases catalyze synthesis of DNA using the four deoxyribonucleotide building blocks dATP, dGTP, dCTP, and dTTP. Cytarabine **11** is considered as one of the most active DNA polymerases inhibitors (Patrick, 2013).



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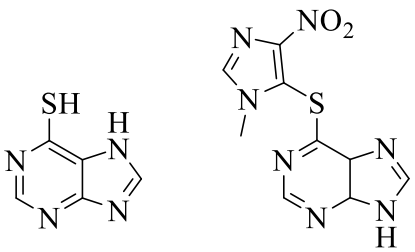
2.3.1.6. Purine antagonists

Purines are integral components of RNA, DNA and coenzymes that are synthesized in proliferation of cancer cells. Therefore, an agent that antagonizes the purine will certainly lead to formation of false DNA. 6-Mercaptopurine **12** and azathioprine **13** are belonging to this class (Patrick, 2013).



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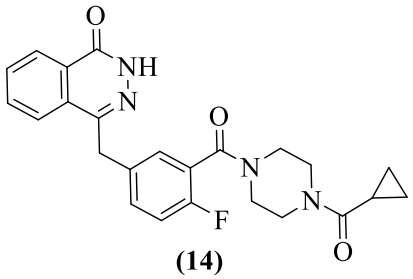
2.3.1.7. Poly-ADP ribose polymerase (PARP) inhibitors

PARP is a highly abundant nuclear protein that is activated when DNA is damaged. PARP1 repairs the single-stranded DNA breaks, predominantly through the base excision repair (BER) mechanism. PARP also contributes to repair double-stranded breaks through non-homologous end joining (NHEJ) pathway, which is further impaired when PARP activity is inhibited (Rouleau, Patel, Hendzel, Kaufmann, & Poirier, 2010). On December 19, 2014, the FDA approved olaparib **14**, an inhibitor of PARP1, as monotherapy for patients with germline BRCA mutated (g BRCAm) advanced ovarian cancer that have been treated with three or more prior lines of chemotherapy (Tangutoori, Baldwin, & Sridhar, 2015).



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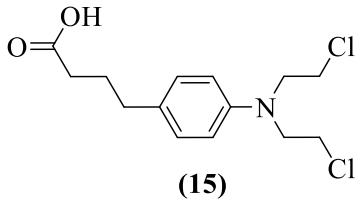
2.3.2. Alkylating agents

Drugs with two alkylating groups can cause cross-linking that disrupts replication or transcription of DNA. Examples of alkylating agents are chlorambucil **15** and carmustine **16** (Patrick, 2013).



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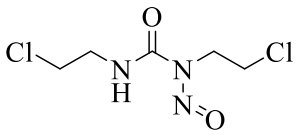

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2.3.3. DNA topoisomerases inhibitors

2.3.3.1. DNA topoisomerases

DNA topoisomerases are a family of enzymes responsible for the cleavage, annealing, and topological state (e.g., supercoiling) of DNA. If the DNA cannot be unwound, transcription of the message cannot occur and cell death results because the corresponding proteins cannot be synthesized (Bailly, 2012; Forterre, Gribaldo, Gadelle, & Serre, 2007). However, there are two types of topoisomerase enzymes, known as Topoisomerase I and II.

2.3.3.1.1. Topoisomerase I (Topo I)

Topoisomerase I (Topo I) enzymes can remove negative supercoils in DNA without leaving damaging nicks. They work by breaking only one strand of DNA (Pourquier & Pommier, 2001).

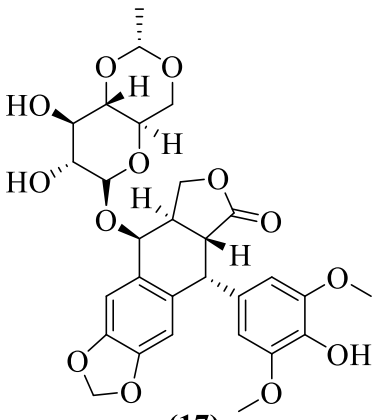
2.3.3.1.2. Topoisomerase II (Topo II)

Topoisomerase II (Topo II) enzymes cleave both strands of double-stranded DNA simultaneously, passing a complete duplex strand through the cut, followed by resealing of both strands (Bodley & Liu, 1988; Sundin & Varshavsky, 1981).

Topo II has been shown to represent the principal targets of effective antitumor drugs (called Topo II poisons) and, hence, has deserved investigation to understand the biochemical and pharmacological basis of drug action (D'arpa & Liu, 1989). Based on insertion into the DNA double strands, Topo II inhibitors are classified into non DNA intercalative and DNA intercalative Topo II inhibitors (Patil & Thakare, 2012).

2.3.3.1.2.1. Non-intercalative topoisomerase II inhibitors

Etoposide **17** (Etopophos® or Vepesid®) is a semisynthetic glucoside of epipodophyllotoxin used to treat small-cell bronchial carcinoma, it works by inhibiting the ability of Topo II to reseal cleaved DNA duplexes. Therefore, normally reversible DNA strand breaks are converted into lethal breaks by processes such as transcription and replication (Chen *et al.*, 1984).



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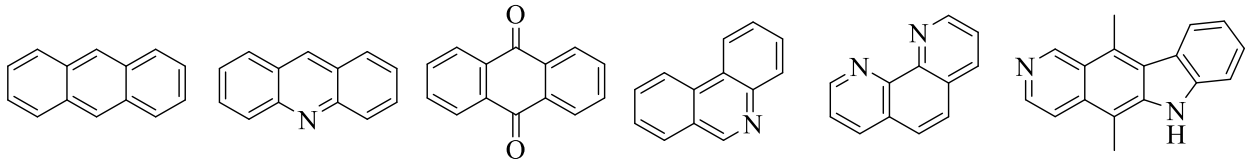
2.3.3.1.2.2. Intercalative topoisomerase inhibitors

Lerman was the first to demonstrate the process of DNA intercalation through his studies into the binding of acridines to DNA (Lerman, 1961). In general, all DNA intercalators have chemical structures based on six different intercalator frame works: anthracenes **18**, acridines **19**, anthraquinones **20**, phenanthridines 2**1**, phenanthrolines **22** and ellipticines **23**.



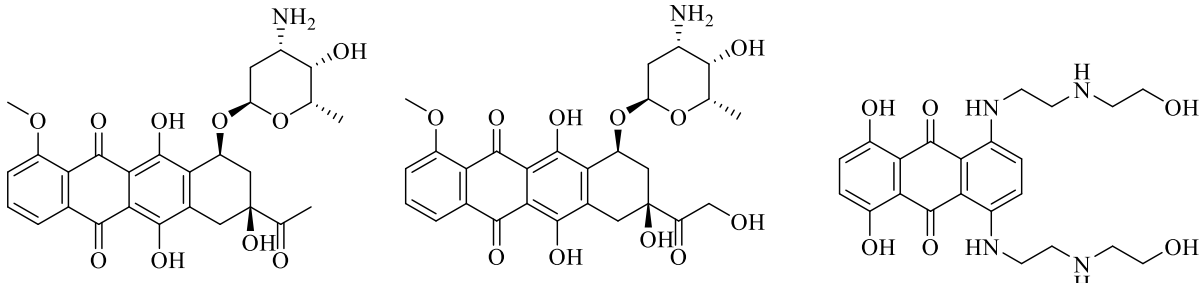
(18) **(19)** **(20)** **(21)** **(22)** **(23)**

Currently there are four organic intercalators approved by the FDA for the treatment of human cancers. Daunorubicin **24** used in the treatment of non-lymphocytic leukemia in adults and acute lymphocytic leukemia in children and adults (Goldin *et al.*, 1981; Hirschfeld, Ho, Smith, & Pazdur, 2003; Wheate, Brodie, Collins, Kemp, & Aldrich-Wright, 2007).

Doxorubicin **25** used in the treatment of a large number of human cancers (Goldin *et al*., 1981) e.g., acute lymphoblastic leukemia, acute myeloblastic leukemia, neuroblastoma, soft tissue and bone sarcoma, and breast carcinoma.

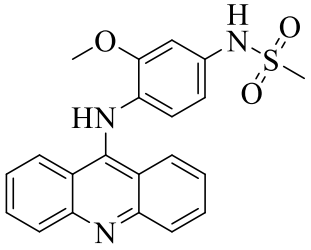
The fact that daunorubicin **24** has such a limited range of effectiveness in the treatment of cancers compared to doxorubicin **25** is surprising, although the two intercalators only differ in structure by one functional group (H for daunorubicin versus OH for doxorubicin).

Mitoxantrone **26** is primarily used to treat multiple sclerosis (MS) but is also used in conjunction with other anticancer drugs for the initial treatment of acute non-lymphocytic leukemia in adults (Cheng, Zbinden, & Zee-Cheng, 1979; Koeller & Eble, 1988; Murdock *et al*., 1979).



(24) **(25)** **(26)**

Amsacrine **27** has previously been used to treat acute adult leukemia and malignant lymphomas, but it has poor activity in the treatment of solid tumors, and is classified by the FDA as an orphan drug (Sung *et al*., 2005).



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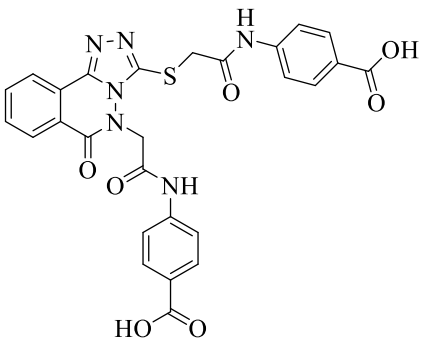
These organic drugs all bind by intercalation from the DNA minor groove (Plumbridge, Knight, Patel, & Brown, 1980), although some, like mitoxantrone, have also been shown to bind DNA by non-intercalating electrostatic interactions (Denny & Wakelin, 1990; Islam *et al*., 1985; Kapuscinski & Darzynkiewicz, 1985; Lown, Morgan, Yen, Wang, & Wilson, 1985; Murdock *et al*., 1979). Recently, researchers have synthesized new organic intercalators, examined ways to increase the localization of organic intercalators in cancer cells and studied the interactions of organic intercalators with DNA to a much greater extent than before.

In 2020, Eissa *et al*., designed and synthesized a series of phthalazine derivatives as Topo II inhibitors and DNA intercalators. The synthesized compounds were *in vitro* evaluated for their cytotoxic activities against HepG-2, MCF-7 and HCT-116 cell lines. Additionally, Topo II inhibitory activity and DNA intercalating affinity were investigated for the most active compounds. Compounds **28, 29,** and **30** exhibited the highest activities against Topo II.



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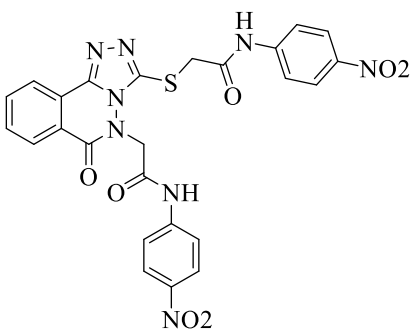

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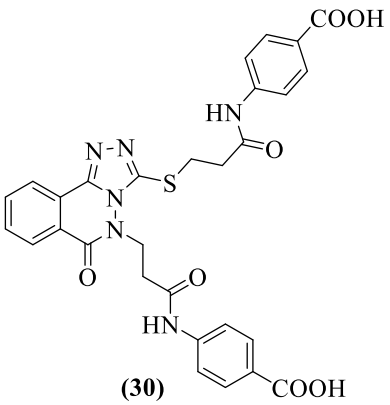

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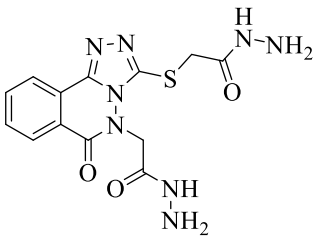

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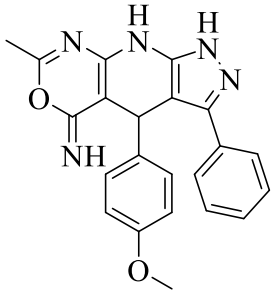
In 2016, a new series of 1*H*-pyrazolo[3,4-*b*] pyridine derivatives were designed and synthesized. The anti-proliferative activity of the newly synthesized compounds was evaluated against HePG-2, MCF-7, HCT-116, and PC-3 cell lines. Additionally, DNA binding affinity of the synthesized derivatives was investigated as a potential mechanism for the anticancer activity. Compounds **32** and **33** exhibited good activity against the four cancer cells comparable to that of doxorubicin (Eissa, El-Naggar, & El-Hashash, 2016).



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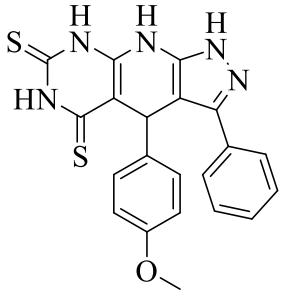

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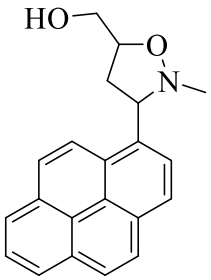
Rescifina *et al*., have synthesized a series of isoxazolidinyl intercalators, among them, compound **34** displayed the highest cytotoxicity in MOLT-3, THP-1, U937 and Vero cell lines (Rescifina *et al*., 2006).



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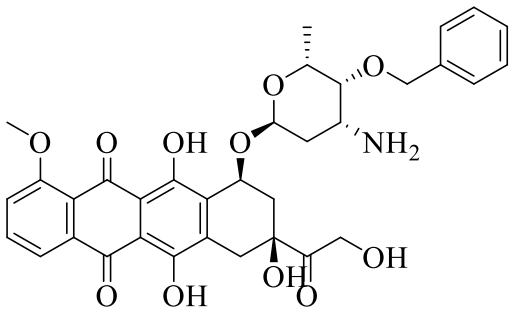
Inge *et al*., have designed and synthesized doxorubicin derivatives to overcome multi-drug resistance (Inge, Harris, Wu, Azizkhan, & Priebe, 2004). Two of these drugs (WP744 **35** and WP769 **36**) were found to be 2 to 36 times more active than doxorubicin in the advanced neuroblastoma cell lines tested.



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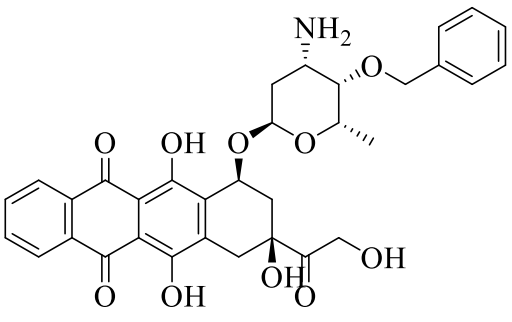

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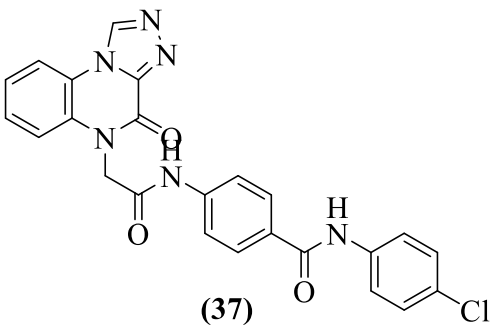
3. Quinoxaline derivatives as anticancer agents

In 2021 Alsaif *et al*., designed, synthesized a new series of [1,2,4] triazolo[4,3-*a*]quinoxalin-4(5*H*)-one and [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives and biologically assessed for their anti-proliferative activities against two selected tumor cell lines MCF-7 and HepG2. Comparing to doxorubicin (IC_{50} = 2.17 and 3.51 µM against MCF-7 and HepG2, respectively), compound **37, 3 8, 39,** and **40** exhibited the highest activities against the examined cell lines with IC_{50} values extending from 4.1 to 11.7 µM.



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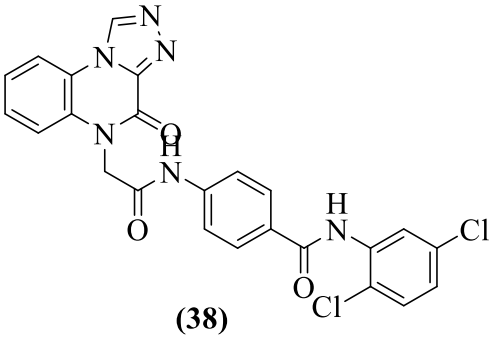

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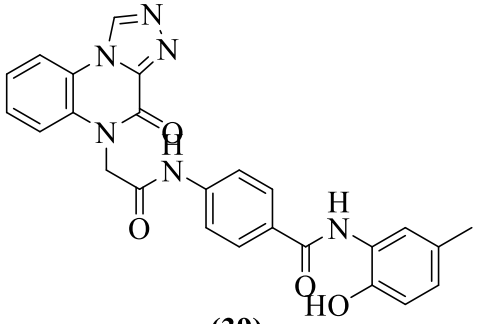

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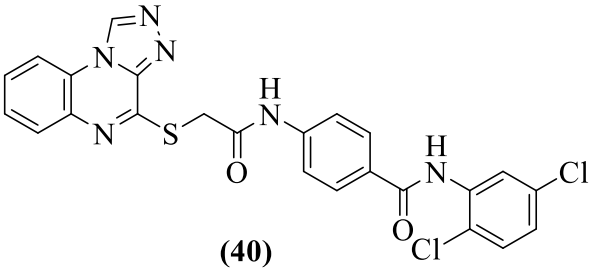
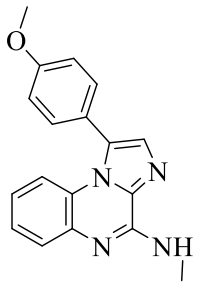
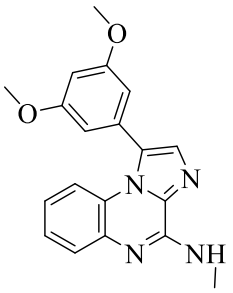


(40)

In 2016 Zghaib and co-worker designed and synthesized imidazo[1,2-*a*]quinoxaline derivatives and the anticancer efficacy of 13 novel derivatives on A375 human melanoma cell line. All new compounds show significant antiproliferative activity with IC_{50} in the range of 0.077–122 µM against A375. Direct inhibition of tubulin polymerization assay *in vitro* was also assessed. Results show that compounds **41**, **42**, **43**, and **44** highly inhibit tubulin polymerization with percentages of inhibition of 99%, 98%, 90%, and 84% respectively (Zghaib *et al*., 2016)



(41)



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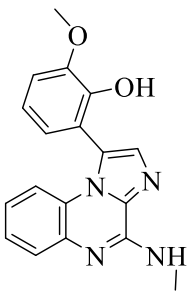

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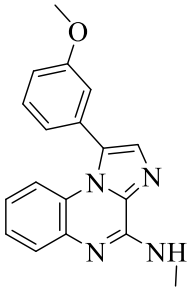
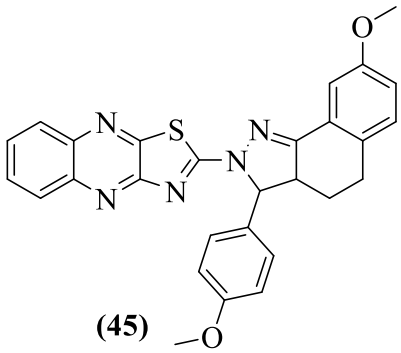


(44)

In 2015, Zong *et al*., designed and synthesized twenty-five pyrazole–quinoxaline derivatives, their biological activity as potential EGFR or HER-2 kinase inhibitors. Among them, compound **45** displayed better antiproliferative activity against A549 and MCF-7 cell lines than **Erlotinib** With IC_{50} value of 3.04 μM, 1.91 respectively (Zong *et al*., 2015).

In 2015, Abbas *et al*., designed and synthesized Some new quinoxaline derivatives, studied as inhibitors of c-Met kinase, a receptor associated with high tumor grade and poor prognosis in several human cancers. Compounds **46**, **47**, showed the lowest IC_{50} values against MCF-7, NCI-H460, and SF-268, than Doxorubicin (Abbas, Al-Marhabi, Eissa, & Ammar, 2015).



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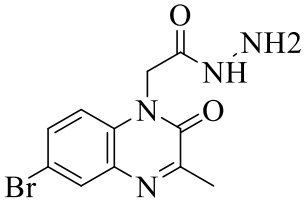

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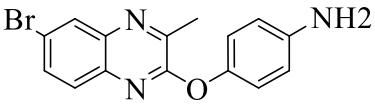
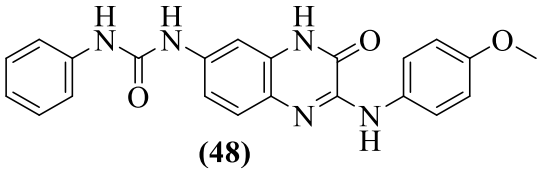


(47)

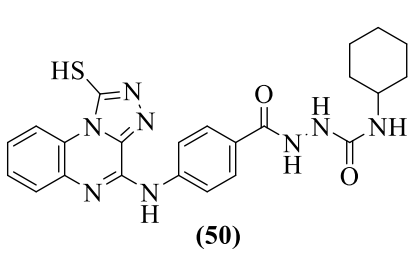
In 2014, Shahin *et al*., exert an effort to develop ATP-competitive TOPO II selective inhibitors, a series of new quinoxaline-based derivatives was designed and synthesized. The target compounds were biologically evaluated for their inhibitory activity against TOPO II. Compound **48** displayed the highest inhibitory activity against TOPO II With IC_{50} value of 10.27 μM (Shahin, Abou El Ella, Ismail, & Abouzid, 2014).



(48)

4. Quinoxaline derivatives as DNA-Topo II inhibitors and DNA intercalators

In 2020, el-adl *et al*., designed, synthesized novel twenty-four [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives and evaluated against HepG2, HCT116 and MCF-7 as DNA intercalators and Top II enzyme inhibitors. Compounds **50**, **51** and **52** were found to be the most potent derivatives (El-Adl, El-Helby, Sakr, & Elwan, 2020).



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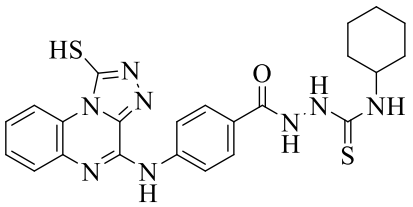

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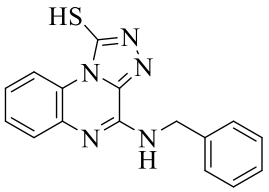
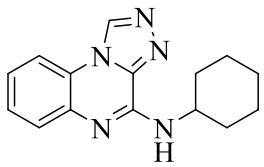


(52)

In 2018, Eissa *et al*., designed, synthesized a new series of [1,2,4]triazolo[4,3-*a*]quinoxaline and bis([1,2,4]triazolo)[4,3-*a*:3',4'-*c*]quinoxaline derivatives and biologically evaluated for their cytotoxic activities against HePG-2, Hep-2 and Caco-2. Compounds **53, 54, 55** and **56** exhibited the highest activities against the examined cell lines with IC_{50} values ranging from 0.29 to 0.90 µM comparable to that of doxorubicin (IC_{50} ranging from 0.51 to 0.73 µM) (Ibrahim *et al*., 2018).



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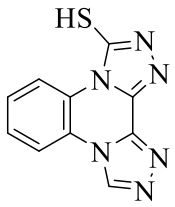

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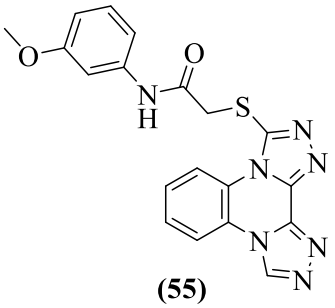

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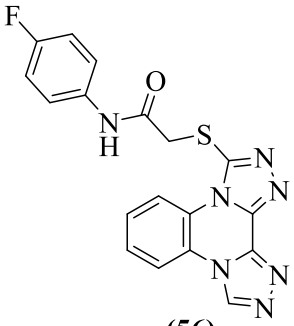
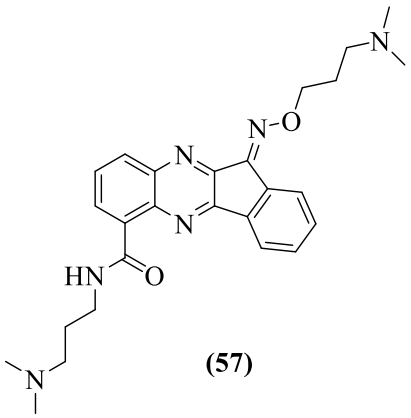


(56)

Hua Tseng *et al*., in 2016 synthesized certain indeno[1,2-*b*]quinoxaline derivatives for antiproliferative evaluation. Among them, compound **57** was active against the growth of MDA-MB231, PC-3, and Huh-7. They have also implanted human hepatocellular carcinoma cells into the yolk sac of zebrafish larvae and treated larvae with various concentrations of **57**. Results of the zebrafish xenograft assay confirmed the anti-tumor effect of **57** *in vivo (Tseng et al., 2016).*



(57)

5. Conclusion:

Quinoxaline scaffold was considered as an important class of bicyclic

N-heterocycles, have received considerable attention due to their beneficial biological and pharmacological activities. quinoxalines play a significant role in medicinal chemistry and have emerged as a pharmacophore. The quinoxaline ring is a crucial pharmacophoric scaffold present in the core structures of numerous anticancer molecules with potent activity against hepatocellular carcinoma, colon cancer, and breast cancer. Many studies were reported in the synthesis of several quinoxaline derivatives as promising anticancer agents as powerful topo II inhibitors. According to this review, quinoxaline is a major biological active pharmacophore in medicinal chemistry, as well as a new lead scaffold for safe and effective drugs.

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نظرة على الخصائص الطبية لسقالة الكينوكسالين، مع التركيز على خصائصها المضادة للسرطان كعوامل متداخلة للحمض النووي

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الملخص

تعد الخصائص المضادة للأورام للمركبات الحلقية غير المتجانسة الاصطناعية من بين أقوى الخصائص التي يمكن استخدامها في الكيمياء الطبية. وبشكل أكثر تحديدا ، آثارها السامة للخلايا الكبيرة ضد العديد من أنواع الخلايا السرطانية البشرية ، وكذلك أدوارها كمثبطات للتوبوايزوميراز. في السنوات الأخيرة ، جذبت مشتقات كينوكسالين في كثير من الأحيان اهتمام الباحثين في الكيمياء الطبية بسبب خصائصها الواعدة المضادة للسرطان. الدراسة الحالية هي مراجعة لأحدث التطورات في الأبحاث المتعلقة بمشتقات الكينوكسالين، مع التركيز على كيفية تصنيع هذه المشتقات وعلى أنشطتها المضادة للسرطان كعوامل متداخلة مع الحمض النووى.

الكلمات الرئيسية: مضاد للسرطان ، كينوكسالين ، عوامل متداخلة مع الحمض النووى، توبوازوميراز.