DRUGS AND THEIR MODE OF ACTION: A REVIEW ON HETEROCYCLIC COMPOUNDS AS ANTI-CANCER DRUG AGENTS

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Abstract:
The largest, as well as most diverse categories of organic compounds are made up of heterocyclic compounds. Since there has been so much synthetic research done on them and because of their usefulness in synthetic processes, there are currently many heterocyclic compounds that are known. Despite great developments in cancer treatment, carcinoma continues to rank among the leading causes of death worldwide. Because more individuals are embracing unhealthy lifestyles that include poor diets, frequent smoking, and lower levels of physical activity, the impact of cancer will likely increase in the future. Numerous anti-cancer medications now on the market have heterocycles as important structural elements. This review study includes a list of various heterocyclic substances that are now being sold as anti-cancer medications.

Keywords: Anti-cancer drugs, carcinoma, heterocyclic compound, ADT, GnRH, EGFR.

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1. INTRODUCTION

Heterocyclic compounds have emerged as a prominent class of molecules in the development of anti-cancer drugs[1]. With their diverse chemical structures and unique pharmacological properties, these compounds offer promising avenues for the discovery and design of effective therapeutic agents for the treatment of cancer[2]. This review aims to provide an overview of the role of heterocyclic compounds as anti-cancer drug agents, highlighting their structural diversity, mechanisms of action, and recent advancements in this field[3].The incidence of cancer continues to rise globally, necessitating the development of novel and targeted therapies to combat this devastating disease. Heterocyclic compounds, characterized by the presence of one or more hetero-atoms (such as nitrogen, oxygen, or sulfur) within a ring structure, have shown significant potentials as anti-cancer agents[4]. This incorporation of hetero-atoms in these compounds imparts unique electronic and steric properties, enabling specific interactions with molecular targets involved in cancer progression[5].One of the key advantages of heterocyclic compounds is their structural diversity. The presence of hetero-atoms allows for a wide range of modifications and substitutions on the ring structure, resulting in a vast library of compounds with diverse shapes, sizes, and functional groups[6]. This structural diversity facilitates the exploration of different chemical space, enabling researchers to optimize the interactions between the drug and its target, thereby enhancing potency and selectivity[7].

Heterocyclic compounds have demonstrated diverse mechanisms of actions in their anti-cancer activities. These mechanisms include the inhibition of crucial enzyme involved in cancer cell growth and proliferation, disruption of signalling pathways essential for cancer progression, induction of apoptosis (programmed cell death), inhibition of angiogenesis (formation of new blood vessels), and modulation of DNA repair processes[8]. By targeting specific molecular pathways, heterocyclic compounds can effectively disrupt the survival and growth of cancer cells, while minimizing the impact on normal cells[9].Cancer cells can develop resistance to conventional therapies, rendering them ineffective. Heterocyclic compounds can be designed to target alternative molecular pathways or specific genetic mutations associated with drug resistance, offering new strategies to combat resistance and improve treatment outcomes for patients[10].In recent years, significant advancements have been made in the design and synthesis of heterocyclic compounds as anti-cancer drug agents. The integration of computational modelling, structure-activity relationship studies, and high-throughput screening techniques has accelerated the discovery and optimization of lead compounds [11]. Rational drug design approaches, guided by insights from molecular biology and cancer genomics, have facilitated the development of highly potent and selective heterocyclic anti-cancer agents[12].

Additionally, the field of heterocyclic anti-cancer drug research has witnessed notable progress in drug delivery strategies. The conjugation of heterocyclic compounds with nanomaterials, polymers, or targeting ligands allows for improved drug solubility, stability, and site-specific deliver to cancer cells. This enhances the therapeutic efficacy while minimizing off-target effects and reducing systemic toxicity[13].In this review, we will explore various heterocyclic compounds that have shown anti-cancer potential, including pyrimidines [14], pyridines[15], purines [16], imidazole[17], benzimidazoles [18], pyrazoles[19], and many other. We will delve into their chemical structures, mechanisms of action, and preclinical and clinical studies evaluating their anti-cancer efficacy. Furthermore, we will discuss recent developments in the design and optimization of heterocyclic anti-cancer agents, as well as challenges and future directions in this field. Overall, the exploration of heterocyclic compounds as anti-cancer drug agents represents an exciting and rapidly evolving area of research. Their structural diversity, diverse mechanisms of action, potential for overcoming drug resistance, and advancements in drug delivery strategies make them promising candidates for the development of effective and targeted therapies against cancer[20].

2. THE ROLE OF HETEROCYCLES IN ANTI-CANCER DRUG DESIGN

Heterocycles play a crucial role in anti-cancer drug design due to their unique chemical properties and diverse structural characteristics. These cyclic compounds, containing at least one non-carbon atom (such as nitrogen, oxygen, or sulfur) in the ring structure, offer a versatile platform for the development of potent and selective anti-cancer agents[20]. Here, we explore the important role of heterocycles in the design of anti-cancer drugs.

2.1. Structural diversity:

Heterocycles provide a wide array of structural diversity, allowing medicinal chemists to create libraries of compounds with different shapes, sizes, and functional groups. This diversity enables researchers to explore various chemical space and optimize the drug's interaction with its target, leading to improved potency and selectivity[21].

2.2. Target selectivity:

Heterocycles can be tailored to specifically target certain biomolecules or heterocyclic structure, researchers can design drugs that interact with specific receptors, enzymes, or DNA sequences, thereby inhibiting the aberrant signalling path ways involved in cancer progression[22].

2.3. Drug metabolism:

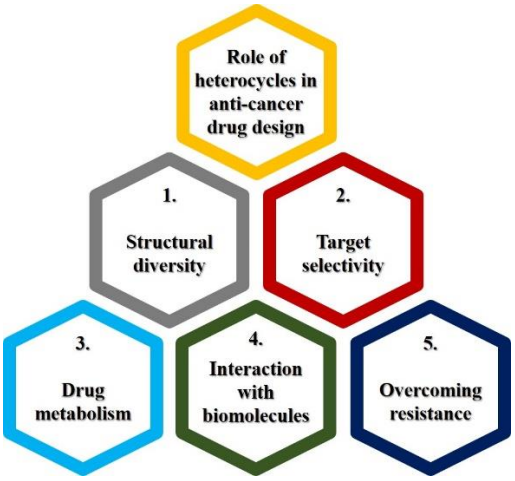
The presence of heteroatoms in the ring structure significantly influences the drug's metabolism and pharmacokinetic properties. Heterocycles can impact the drug's solubility, stability, and bioavailability, allowing for optimization to achieve desired pharmacokinetic profiles, such as improved absorption, distribution, and elimination [23].

2.4. Interaction with biomolecules:

Heterocycles possess diverse electronic and static properties, allowing them to interact with various biomolecules. Through hydrogen bonding, electrostatic interactions, and π-π stacking, heterocycles can bind to specific protein targets or DNA, disrupting vital cellular processes and inhibiting cancer cell growth[24].

2.5. Overcoming resistance:

Heterocycles have been instrumental in overcoming drug resistance in cancer treatment. By targeting specific molecular pathways or mutations involved in drug resistance mechanisms, heterocyclic anti-cancer drugs can overcome resistance and provide alternative treatment options for patients who have failed conventional therapies[25].



The versatile nature of heterocycles makes them valuable building blocks for the design and synthesis of anti-cancer drugs. Their ability to modulate target selectivity, pharmacokinetic properties, and overcome drug resistance makes heterocyclic compounds a promising avenue in the ongoing pursuit of effective and targeted cancer treatments[26].

3. MOTIVATION AND PURPOSE OF STUDY

The motivation and purpose of studying synthetic heterocyclic compounds as anti-cancer drugs stem from the urgent need for effective and targeted treatment for cancer[27]. Cancer is a complex disease characterized by uncontrolled cell growth and the ability to invade surrounding tissues and metastasize to other parts of the body[28]. Conventional cancer treatments, such as surgery, radiation therapy, and chemotherapy, often come with significant side effects and limitations. Synthetic heterocyclic compounds offer several advantages that make them attractive candidates for anti-cancer drug development[29]. Firstly, their diverse chemical structure provides a wide range of possibilities for designing molecules that can specifically target and interact with key cellular components involved in cancer progression. This allows for the development of drugs that selectively inhibit cancer cells while minimizing damage to healthy tissues[30]. Secondly, the synthetic nature of these compounds enables researchers to modify their structures and properties, optimizing their pharmacokinetics and pharmacodynamics. This allows for the enhancement of drug potency, selectivity, stability, and solubility, thereby increasing their effectiveness in treating cancer [31]. The study of synthetic heterocyclic compounds also addresses the challenge of drug resistance in cancer treatment. Cancer cells can develop resistance to traditional therapies,

rendering them ineffective[32]. Synthetic heterocyclic compounds offer the potential to target alternative molecular pathways and overcome drug resistance mechanisms, providing new treatment options for patients who have failed conventional therapies[33].

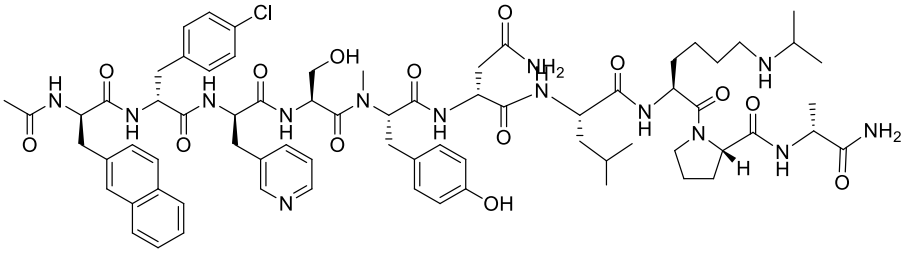
4. SYNTHETICHETEROCYCLICANTI-CANCERDRUGS

Synthetic heterocyclic anti-cancer drugs have emerged as a significant class of pharmaceutical compounds in the field of oncology[34]. These drugs are designed and synthesized with primary aim of targeting and inhibiting specific molecular pathways involved in cancer cell growth and proliferation. Heterocyclics compounds, characterrized by the presence of at least one non-carbon atom within ring structure, offer a diverse range of chemical scaffolds that can be modified to achieve desirable pharmacological properties [35].The development of synthetic heterocyclic anti-cancer drugs has revolutionized cancer treatment by providing novel therapeutic options with improved efficacy and reduced side effects [36]. These drugs act through various mechanisms, such as inhibiting DNA replication, disrupting cell signalling pathways, introducing apoptosis (programmed cell death), and inhibiting angiogenesis (formation of new blood vessels) [37].Researchers have focused on the synthesis and optimization of heterocyclic compounds due to their ability to selectively target cancer cells while sparing healthy cells[38]. This selectivity is achieved by exploiting differences in the molecular pathways and metabolic processes between cancer cells and normal cells[39]. Researchers employ rational drug design strategies to optimize pharmacokinetic and pharmacodynamic properties, such as bioavailability, solubility, stability, and target selectivity [29]. Moreover, synthetic heterocyclic anti-cancer drugs have also shown promise in overcoming drug resistance, a major challenge in cancer treatment[40]. By targeting specific molecular aberrations and genetic mutations present in drug-resistant cancer cells, these compounds offer potential solutions to combat resistance and improve patient outcomes[38].

In this review article, we will explore a selection of different types of anti-cancer heterocyclic drugs, highlighting their mechanisms of action, their specific dosage for patients, as well as their therapeutic application. By understanding the mechanism of action and therapeutic applications of these drugs, researchers can contribute to develop innovative and targeted treatments to improve outcomes for cancer patients. These following examples represent just a fraction of the diverse range of heterocyclic compounds used in cancer treatment.

4.1. Abarelix

A synthetic decapeptide is known as abarelix for injectable suspension with the chemical formula acetyl-D-naphthyl-D-4-chlorophenyl-D-3-pyridyl-alanyl-L-seryl-L-N-methyltyrosyl-D-asparagyl-L-leucyl-L-N(ε)-isopropyl-lysyl-L-pro Alanyl-D-alanine (Figure 1)[41].



Abarelix (183552-38-7)

1

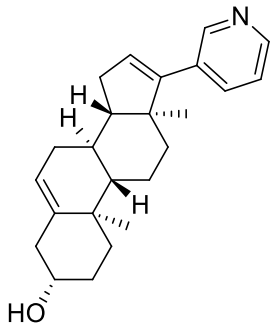
The very initial GnRH antagonist licenced for the medical management of males with advanced as well as symptomatic prostate cancer is called Abarelix. Abarelix lowers the quantity of testosterone generated by the testes by directly blocking the production of luteinizing hormone (LH) with the hormone follicle-stimulating hormone (FSH). Although abarelix immediately decreases LH secretion [^{125}I]-abarelix exhibits a greatly enhanced affinity (KD = 0.1 nM) for the rat pituitary LHRH receptor, as shown by saturation binding studies, there is zero immediate spike in serum testosterone levels[42].

A persistent subcutaneous infusion of abarelix is being investigated in open-label research on over the course of 84 days (12 weeks), 36 adult males with therapeutically localised or regional prostate cancer were diagnosed[43]. Each patient received

treatment for a minimum of 28 days (4 weeks) at a dosage of 50 mgper day. Testosterone, dihydrotestosterone, follicle-stimulating hormone, prostate-specific antigen, and luteinizing hormone were tested before and after administration to assess the pharmacologic effects of Abarelix[44].

4.2. Abiraterone

In contrast to ADT alone, ADT + abiraterone and prednisolone was linked with considerably higher probabilities of but also failure-free survival in adult male having locally advanced or metastatic prostate cancer[45].Abirateronetherapy causes androgen creation inside the suprarenal glands or perhaps within the tumour itself to be completely and quickly inhibited ADT was administered for at least two years; radiation was required for those with a node-negative, nonmetastatic disease as well as choice for people with node-positive, nonmetastatic disease at 6 to 9 months shortly after randomization[46]. Prednisolone (5 mg) and abiraterone (1000 mg) were administered once daily. The length of treatment was determined by the disease state and the plan for radical radiotherapy. Abiraterone acetate is administered by mouth and is a potent inhibitor of cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17), required for testosterone synthesis via cholesterol[47].



Abiraterone (154229-19-3)

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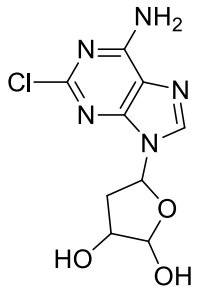

Cladribine (2-CdA) (4291-63-8)

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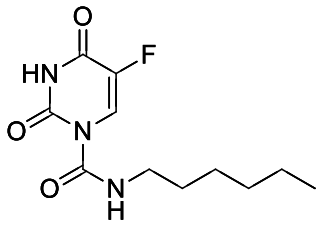

Carmofur (61422-45-5)

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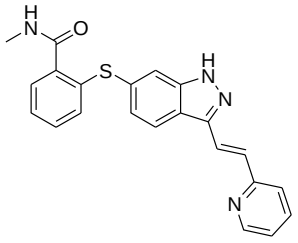
4.3. Cladribine

Hairy cell cancer Leukaemia is an uncommon chronic B-cell lymphoproliferative disease that is distinguished by mononuclear cells with cytoplasmic projections[48]. Patients received a continuing intravenous infusion of cladribine in individual sessions. Beginning from June 1991, Ortho Biotech began giving Cladribineto patients at the dosage of 0.1 mg daily for seven days. It was initially developed at Scripps Clinic and given at a dosage of 0.087 mg per kilogram of body weight daily over seven consecutive days (patients 1 to 224)[49]. Chloro-adenine's extinction coefficient was somewhat smaller compared to cladribine' and used to standardize the medication that was synthesized at Scripps Clinic. As a result, only 87% of the planned dose was administered[50].

4.4. Carmofur

used for treating gastrointestinal cancer and solid cancers such as glioblastoma and melanoma [51]. Carmofur, also known as 1-hexyl carbamoyl-5-fluorouracil (HCFU), is a strong chemotherapy medication that is used for treating different tumours[52].The term of cell growth & metastasis associate proteins, as well as the viability of tissues, apoptosis, colony development, migration, and invasion, were all analysed after a 0–1 g/mL of HCFU therapy for 0–48 hours[53].Since it has been used in clinical settings since 1981, carmofur considerably improves colon cancer patients' overall survival including disease-free survival rates. Moreover, carmofur looks beneficial against colorectal, bladder, stomach, and breast malignancies[54].



Axitinib (319460-85-0)

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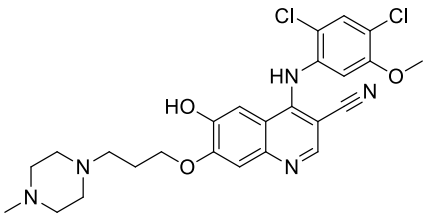

Bosutinib (380843-75-4)

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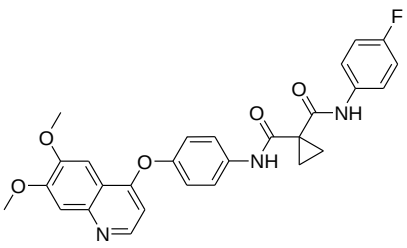

Cabozantinib (1817759-42-4)

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4.5. Axitinib

Axitinib (AG-013736) is an oral as well astargeted tyrosine kinase inhibitor as well as applied for treating renal cell carcinoma. Several solid tumours have seen potential action with axitinib[55].During a 4-week lead-in phase, people who had metastatic renal-cell carcinoma who did not have prior treatment were given Axitinib, 5 mg twice daily[56]. Depending on an Eastern Cooperative Oncology Group evaluation of effectiveness (0 vs. 1), patients were split into two groups, and then they received their groups at random (1:1) to either receive concealed axitinib titration to total twice-daily dosages of 7 mg, coupled with the 10 mg, if tolerated, or placebo titration[57]. Axitinib showed a favourable safety profile and encouraging anticancer efficacy when used in conjunction with docetaxel as the first therapy treating metastatic breast cancer[58].

4.6. Bosutinib

Bosutinib (SKI-606), an oral-pill based Src and Abl kinase inhibitor, is now undergoing phase III trials for the therapeutic management of breast cancer and chronic myelogenous leukaemia (CML) as well as used in the therapy for chronic myelogenous leukaemia[59]. With nano-molar concentrations, bosutinib suppresses Bcr-Abl-mediated signaling and is a powerful antiproliferative along with a proapoptotic agent in CML cells. Patients with CML are advised to take 500 mg of bosutinib once every day with food. Bosutinib is largely metabolised via cytochrome P450 (CYP) 3A4 and eliminated primarily in faeces[60].In feeding situations, bosutinib uptake is linear & dose-proportional across the whole 200–800 mg investigated dosage range. The average terminal elimination half-life varies from 32 and 39 hours, whereas the median time for a peak plasma concentration in normal adult participants is around 6 hours[61].

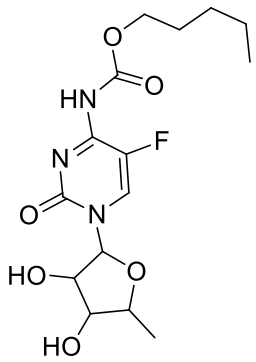
4.7. Cabozantinib

Used to deal with advanced hepatocellular carcinoma, lung cancer, prostate cancer, modularly thyroid cancer, and advanced renal cell carcinoma[62]. Cabozantinib, an oral, small-molecule, multi-targeted TKI, may provide a benefit over traditional TKIs that solely target one receptor. Given that single-target TKI use frequently results in tumour resistance, the ability to target numerous kinases may be preferable to medicines with a single target[63].

4.8. Afatinib

The treatment alternatives to advanced non-small cell lung cancer (NSCLC) have surely increased because of the intriguing new drug afatinib. Especially for individuals having pulmonary adeno-carcinomas that have somatic EGFR (epithelial growth factor receptor) mutations [64]. Grade 3 issues, such as diarrhoea and rashes, were significantly more prevalent in people receiving a

50 mg starting amount rather than they are in person's obtaining a 40 mg beginning dose, based on the second phase of the LUX-Lung 2 investigation. Although there was not significant variation in adverse events (AEs) over the cohorts administered with different dosages of afatinib in Phase IIb/III LUX-Lung 1 along with LUX-Lung 3, many patients in LUX-Lung 1 required dose reduction and discontinuation[65].



Afatinib (850140-72-6)

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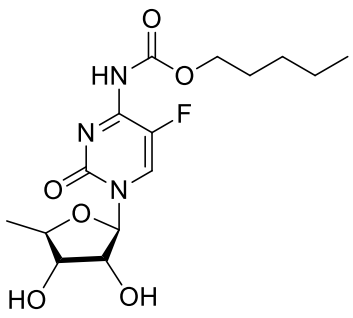

Capecitabine (154361-50-9)

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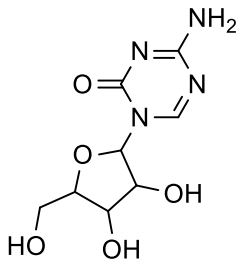

Azacitidine (5-azacytidine) (320-67-2)

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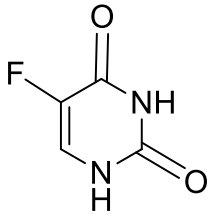
4.9. Capecitabine

Through the transformation of tumour-specific active agents, to enhance the tolerability & intra-tumour medication levels, capecitabinewas designed as a pro-drug of FLUOROURACIL (FU) and used to deal with pancreatic, prostate, breast cancer, renal cell carcinoma, colon, ovarian, and rectal types[66].It has shown varying levels of action in a few cancers while being tolerable 33 participants signed up for the study. There were few negative effects at or below 1,331 mg/m^2/d. Palmar-plantar erythrodysesthesia, nausea, vomiting, vertigo, stomach discomfort, diarrhoea, and thrombocytopenia were toxicities that were restricted[67]. There were 1,657 mg/day of MTD, each toxicity was reversible. One breast cancer patient had a variable reaction. Pharmacologic tests revealed that the parent drug was rapidly and extensively metabolized which has a maximum plasma concentration (Cm) that is metabolised into lethal metabolites occurring one hour after intake. With linear increments in the administered dose, the region underneath the concentration-time curve (AUC) and C_{max} both showed linear increases[68].

4.10. Azacitidine

A ribonucleoside, azacitidine works by inhibiting DNA methyltransferases. Since it gets incur-porated in RNA as well as DNA, it serves a multitude of purposes. Azacitidine has the additional function of inhibiting protein production since it is incorporated into RNA as well as used as a myelodysplastic syndrome (MDS) therapeutic [69].Myeloid cell differentiation dysplasia, inadequate hemato-poiesis, refractory cytopenia, hematopoietic function failure, and an increased risk of developing acute myeloid leukaemia are all features of the myelodysplastic syndrome (MDS) [70]. An efficient treatment strategy was to begin with a dosage of 75 mg/day by azacitidine and gradually increase it over the course of the subsequent cycles. In majority of the treatment cycles prior to attaining a response, approximately 46% of patients with the greatest CRs or PRs got 75 mg/day, 37% got less than 75 mg/day, and 17% experienced over 100 mg/day[71].



5-Fluorouracil (51-21-8)

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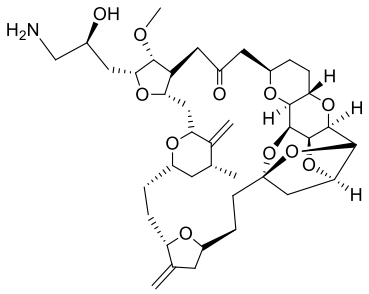


Eribulin (253128-41-5)

12

4.11. 5-Fluorouracil

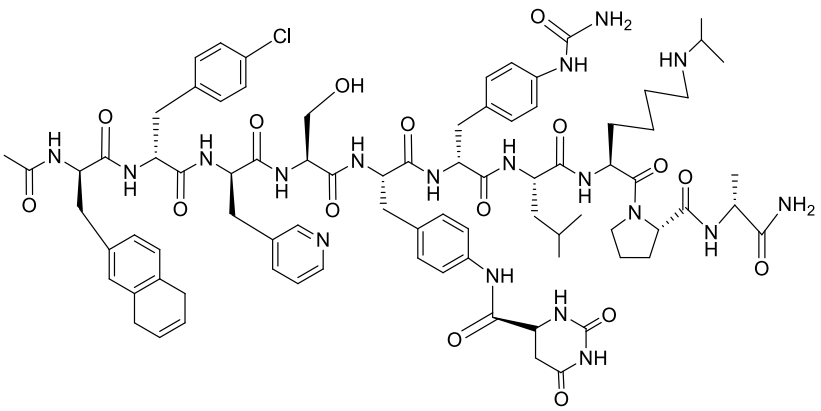
Thymidylate synthase (TS) inhibition, results in the depletion of the intracellular deoxy-nucleotide that stores needed for DNA replication which is the primary mechanism by which 5-FU delivers its anticancer effects as well as used to treat advanced colorectal cancer. Other possible mechanisms for action includes incorporation into DNA, that would result in DNA fragmentation, and incorporation in RNA (where it would replace over fifty percent of uracil), which might halt RNA production following its anabolism[72].118 individuals in stage C & 118 individuals in stage Bz were included in this study as subjects. The adjuvant therapy consisted of folinic acid 200 mg/ml intravenously coupled with 5-Fuorouracil 400 mg/ml on instances of 1-5 each four weeks for overall 12 cycles[73]. Despite being one of the safest chemotherapy medications, 5-FU, some CRC patients nevertheless endure significant toxic and side effects, including sickness, exhaustion, oral thrush, stomatitis, nausea, vomiting, & diarrhoea. Other often occurring dangerous side effects include anaemia, neuropathy, leukopenia, neutropenia, throm-bocytopenia, skin rash, and hand-foot syndrome [74].

4.12. Eribulin

Early findings from combined therapy trials show that eribulin is an attractive companion for potential combination regimens and that eribulinmay be well tolerated in such regimens as well as used for the treatment of third-line curative therapy for advanced breast cancer[75].In various human tumour xeno-graft models, which include those of ovarian, breast, colon, melanoma, and glioblastoma tumours, eribulin's in vivo anticancer activity at doses < 0.1-1 mg/kg was also demonstrated[76].Tests conducted both in vivo along with in vitro show consequences for cell cycle arrest, including destruction of the mitotic spindle, which are consistent with tubulin-based anti-mitotic action of halichondrin B. Eribulin works as a non-taxane inhibitor of microtubule dynamics[77].

4.13. Degarelix

A GnRH antagonist called degarelixis employed as a preliminary treatment for advanced, androgen-dependent prostate cancer. Degarelix is a successful and easily tolerated medication for advanced PCa, according to numerous clinical investigations[78].Without the first testosterone surge as well as micro surges linked to GnRH agonists, Degarelix quickly reduces testosterone & prostate-specific antigen (PSA)[79].Based to phase III findings from study CS21, the highest recorded plasma content of degarelix in individuals with PCaafter a single 240 mg administration was 66 mg/ml, while the concentrations' area underneath the curve over time (day 0-28) had been 635 mg/day per ml, & the mean time to C_{max} was 40 h[80]. By modelling population pharmacokinetics, it was predicted that the initial and maintenance dosages' median terminal half-lives were 43 and 28 days, respectively[81].

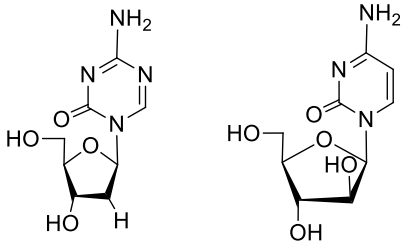


Degarelix (214766-78-6)

13

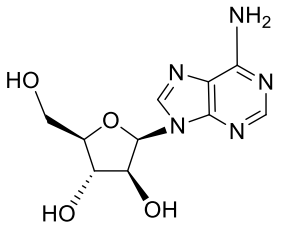
4.14. Decitabine

The epigenetic suppression of those genes that control leukemogenesis brought on by aberrant DNA methylation is the process that ensures 5AZA-CdR delivers its anti-leukemic actions. An S-phase-specific agent is 5AZA-CdR. This variant can cause terminal differentiation including loss of clonogenicity among human leukemic cells at administrations in the micro-molar range[82]. Decitabine was given intravenously over 5 days straight, every second week for a maximum. After each new group was enrolled, there is a 42-day surveillance periodfor accrual. With the first group of four patients, decitabine was started at a dosage of 5 mg/day. As a result of the dose-limiting toxic effect (DLT) that was seen at the prior dose stage, the dose was increased in following cohorts to 7.5, 10, and then 15 mg/day. If a DLT was shown in the first group, the dosage of decitabine could be lowered to 2.5 mg/day. After each new group was enrolled, there is a 42-day surveillance period[83].



Decitabine (2353-33-5) Cytarabine (147-94-4)

14 **15**



Fludarabine (75607-67-9)

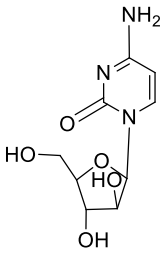
16

4.15. Cytarabine

Cytarabine is commonly applied to treat acute myeloid leukaemia. The factors that can influence leukemic cell survival include high levels of cytidine deaminase, an enzyme which inactivates cytarabine, including drug resistance brought due to shortage of deoxy-cytidine kinase, an enzyme which triggers the prodrug cytarabine[84].In this opinion, several tactics are proposed to boost cytarabine's effectiveness when attempting to treat acute myeloid leukaemia[85].Over the past thirty years, cytarabine has been among the mainstay medications used to treat acute myeloid leukaemia (AML)[86].High dosing of cytarabine (2000 - 3000 mg/m2 of body surface area) were hazardous, but they also resulted with higher rates to relapse-free survival than low doses (100 - 400 mg per square metre)[87].

4.16. Fludarabine

Fludarabine is becoming more utilised as the first line of therapy for low-grade lymphoproliferative cancers like chronic lymphocytic leukaemia (CLL) and follicular lymphoma. In contrast to becoming myelo-suppressive and having been linked to neurotoxicity, fludarabine has a strong immunosuppressive effect[88].Fludarabinewas given to patients either alone or in combination with other chemotherapy medicines; 10 patients received fludarabine orally and 37 received it intravenously. The iv preparation's dosage was 25 mg/m^2 with a similar schedule, while the oral preparation was given at a dose of 40 mg per m^2 every four weeks, given on the first day through 5. Rituximab 375 mg/m^2, mitoxantrone 8 mg/m^2, along cyclophosphamide 250 mg/m^2 were also administered in combination on days 1 through 5. The routine was repeated every four weeks. All the patients were scheduled for up to 6 cycles[89].



Cytosine Arabinoside (147-94-4)

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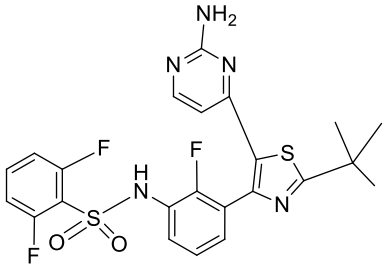


Dabrafenib (1195765-45-7)

18

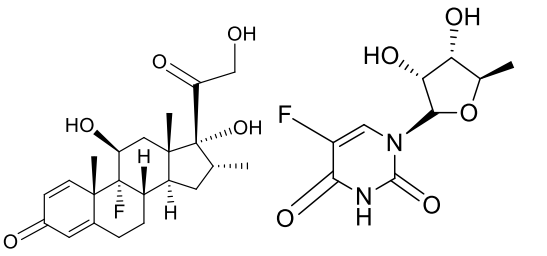
4.17. Cytosine arabinoside

Arabinoside cytosine (ara-C)is used in the management of acute leukaemia is a synthesized

pyrimidine nucleoside in contrast to cytidine and deoxycytidine in that it has a sugar component [90]. It is cytotoxic for mammalian cells in culture, inhibiting several DNA viruses, and poses a threat to mammalian cells. It also demonstrates in vivo anticancer activity against leukaemia and a variety of transplanted rodent neoplasms[91]. Talley and Vaitkevicius documented a group of 13 individuals who had ara-C therapy. These scientists administered the drug intravenously in doses of between 3 and 10 mg/Kg each day from 4 to 9 days. A single dose of 30-50 mg/Kg recited over 7 to 10 days, or a maximum dose of 50 mg/ Kg (with regular injections), was provided[92].

4.18. Dabrafenib

Adenosine triphosphate-competitive inhibitor dabrafenib (GSK2118436) preferentially inhibits the BRAFV600E kinase and is reversible. Five times less medication is needed for BRAFV600E kinase activity to be 50% inhibited (IC50) than it is for BRAFwt or CRAF. In those suffering from metastatic BRAFmut melanoma, Dabrafenibhas a low, tolerable toxicity profile, good response rates, and an improved PFS over chemotherapy; however, the benefit is often fleeting due to the development of acquired resistance[93].In vivo, dabrafenib's brain to AUCplasma (Kp) ratio increased 18-fold in Mdr1 a/b-1-/-Bcrp1-1- mice when an administration of 2.5 mg/kg intravenously was given to them, from 0.023 to 0.42. When given orally at a dose of 25 mg/kg, dabrafenib plasma administration was about 2-fold more prominent in Mdr1 a/b-1-/-Bcrp1-1- mice in contrast to wild-type mice, however the brain allocation was around 10-fold higher, leading in a Kp of 0.25[94].



Dexamethasone (50-02-2) Doxifluridine (3094-09-5)

19 **20**

4.19. Dexamethasone

The most often prescribed glucocorticoid (GC) is dexamethasone(DEX), which has a broad range of pharmacological activities such as used in cancer therapy as antiemetic agent. The non-target organs, however, may experience significant side effects from steroid medications like DEX[95]. Creating targeted systems with one method to decrease these adverse effects is to conjugate to polymeric carriers selected systems with regulated releases. The 20mg dose of dexamethasone proved to be considered as most effective for use when mixed with a 5-HT3 antagonist for preventing *cis*-platin-induced acute emesis in an alternative dose-ranging investigation using only intravenous doses of 4, 8, 12, or 20 mg given forty-five minutes prior to *cis*-platin-based treatment[96].From the individuals who got 4 mg of dexamethasone, 69.2% and 60.9%, respectively, reported being completely free of acute symptoms of nausea and vomiting, 69.1% as well as 61.0% of individuals who got 8 mg, 78.5% and 66.9% of people who got 12 mg of dexamethasone, and individuals who administered 20 mg of dexamethasone were given by 83.2% and 70.0%, respectively[97].

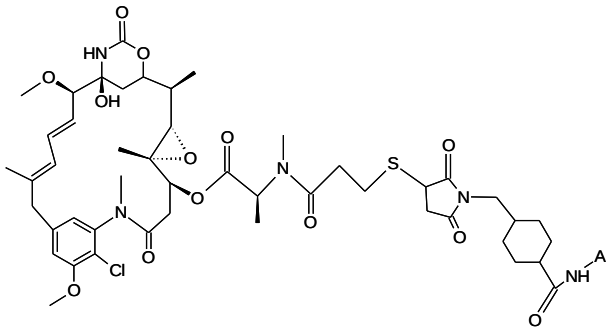
4.20. Doxifluridine

A fluoropyrimidine derivative known as doxifluridine (5'-deoxy-5-fluorouridine; 5'dFUR) exhibits strong anti-tumour efficacy in various experimental animal tumour models as well as utilized for treating squamous cell cancer of the skin and lung carcinomas. This 5-Fluorouracil (5-FU) molecule is joined to a pseudopentose in its chemical structure. In mice, this substance has a very potent anti-tumour impact against Lewis lung carcinoma, Crocker's sarcoma S-180, and a chemically generated cutaneous squamous cell carcinoma [98].Over a phase-I clinical study that included a daily schedule and quick intravenous injections five days in a row, dosages were raised up to 5 g/m^2. The EORTC's clinical assessment of 5'dFUR included a few phase-II trials of advanced colorectal, breast, renal, endometriotic, stomach, & ovarian carcinomas. A dose of 12.5 g/m^2 was continually given over the course of six hours[99]. Out of 173 evaluable patients, consciousness changes and other neurological symptoms were detected in 72.In a phase-III research comparing 5-FU with 5'dFUR, patients with advanced colorectal cancer receiving 5-FU were contrasted to those getting 5'dFUR. There were various administration methods utilized in each of these trials[100]. After the rapid or bolus dosages (0.3-5 g/m^{2}every day for 5 days per 3–4 weeks), there was an elevated level of toxicity. The dose was below 4 g/m^2 of the highest permissible level [101].

4.21. Trasturumab emtansine

The integrated drug trastuzumab emtansine (T-DM1)successfully combines the anticancer effects

of trastuzumab, which are HER2-targeted, along with the cytotoxic effects of the microtubule-inhibitory medication DM1 (a subtype of maytansine) as well as utilised as an aspect of a patient's treatment for metastatic breast cancer [102]. The cytotoxic substance and the antibody are joined via an intact linker[103]. By facilitating intracellular drug delivery to HER2-over expressing cells only, T-DM1 boosts the therapeutic efficacy and reduces exposure to healthy tissue[104]. T-clinical DM1 is effective in treating individuals with advanced breast cancer that is HER2-positive, according to phase 2 research[105].In a single-arm stage II study (TDM4258g), individuals with HER2-positive MBC who experienced growing tumours after having prior HER2-directed treatments and prior chemotherapy had their effectiveness as well as safety of through IV T-DM1 (3.6 mg/kg once every three weeks) evaluated[106].

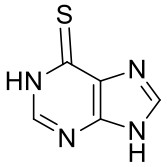


Trastuzumab Emtansine (1018448-65-1)

21

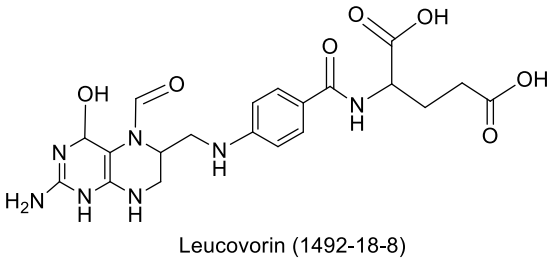
4.22. Mercaptopurine

Acute lymphoblastic leukaemia, in contrast to other malignancies, necessitates protracted treatment, including induction (roughly one month), maintenance and continuation therapy (18–30 months), in addition to post-induction intensification (approximate 6 months)[107].For more than 50 years, the cornerstones of maintenance therapy have been oral mercaptopurinetaken daily and methotrexate is taken once a week[108]. As inhibiting de-novo purine synthesis, methotrexate polyglutamate and methylation mercaptopurine metabolites such as methyl thioinosine monophosphate promote the entry of thioguanine triphosphate into DNA through salvage mechanisms[109].Following diagnosis, at therapeutic weeks 13 (for SR), 32 (for IR), plus 63 (for high threat), maintenance therapy was started and continued for two years (for SR), or two years (for IR in addition to high threat). MTX prescriptions of 20 mg/m^2/week and 75 mg/m^2/day 6MP dosages were utilised to start maintenance therapy. During regular therapy, those suffering from high-risk ALL administered intrathecal MTX (age-adjusted dosages) at intervals of eight weeks, in addition, prednisolone (40 mg/m^2/day over a week) and VCR (1.5 mg/m^2) were reinduced. Even in the initial phases of remission, none of the participants in the group underwent hematopoietic stem cell transplantation [110].



Mercaptopurine (50-44-2)

22



Leucovorin (1492-18-8)

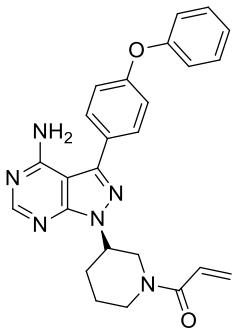
23

4.23. Leucovorin

Leucovorin is quite effective for acute lymphoblastic leukaemia in children (LV), is a reduced form of folate that gets through MTX's blocking of DHFR. By "rescuing" cells that have experienced MTX-induced cell death, it is thought that administering a dose of LV lessens the harmful side effects[111].We previously showed that 20% of patients in a possible cohort of children with ALL developed severe (grade III/IV) MTX-induced through mouth mucositis despite receiving adequate LV rescue therapy. Severe oral mucositis brought on by MTX reduces children's quality of life and may result in treatment delays. Folic acid rescue therapy (Leucovorin - LV), given after HD-MTX infusions, helps to reduce harmful side effects [112]. Leucovorin was initiated 24 hours, 36 hours, or 42 hours following HD-MTX at a dosage of 15 or 30 mg/m^2. Since the treatment strategies varied, no meta-analysis was possible. When examining studies with identical HD-MTX dosages, we discovered lower oral mucositis rates among regimens with higher cumulative amounts of leucovorin coupled with the start of leucovorin after MTX[113].

4.24. Ibrutinib

The effectively inhibited by the small drug ibrutinib is Bruton's tyrosine kinase (BTK) as well as employed for treating chronic lymphocytic leukaemia. By establishing a covalent bond to a cysteine residue (Cys-481) in the binding site of BTK, ibrutinib 85 impairs the enzyme's ability to function[114]. A crucial communication protein of the B-cell antigen receptor (BCR) and cytokine receptor pathways is BTK, certainly among the Tec kinase family members[115]. The critical role of BTK in activating the pathways needed for B-cell adhesion, chemotaxis, & trafficking results from signalling via the B-cell receptors on the surface. Ibrutinib efficiently reduces malignant B-cell multiplication and ability to survive in vivo, but also cell migration and substrate adherence in vitro, according to preclinical investigations [116]. Three capsules, or 420 mg, should be used once daily in therapy of CLL. Until the disease worsens or the patient can no longer tolerate the treatment, it should be continued[117].



Ibrutinib (936563-96-1)

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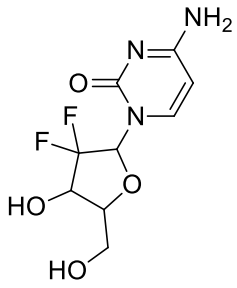

Gemicitibine (95058-81-4)

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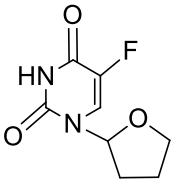


Ftorafur (17902-23-7)

26

4.25. Gemcitabine

Gemcitabine (29,29-difluoro 29-deoxycytidine, dFdC) was initially investigated as a potential antiviral agent, but because of its outstanding anti-tumoural qualities both in vitro and in vivo, it was later developed as a potential anticancer drug [118]. Gemcitabine has shown in a range of solid as well as haematological carcinoma lineages that it can inhibit the metastasis of human cancer, into vivo murine tumour cells, and even human tumour xenografts in nude mice[119].For a total of six courses of therapy, individuals were given either conventional cisplatin MVAC every 28 days or Gemcitabine plus cisplatin (GC) (gemcitabine 1,000 mg/m^2/days 1, 8, and 15 as well as cisplatin 70 mg/m^2/day)[120].

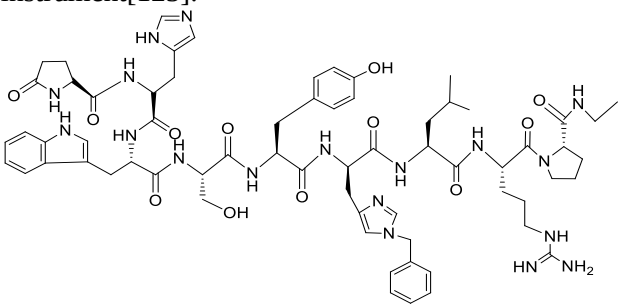
4.26. Ftorafur

Tetrahydrofuranyl-5-fluorouracil, originally developed in 1967 as a precursor to the drug of fluorouracil (5-FU), it is frequently referred to as ftorafur. In living things, ftorafur is converted to 5-FU via the cytochrome P-450 system, thymidine phosphorylase, unregulated break down, especially in the liver microsomes. Ftorafur has generally demonstrated weak anticancer efficacy whether taken orally or intravenously (IV)[121].581 people with colorectal cancer participated in UFT clinical studies that were reported in the West. In these experiments, leucovorin (LV) has either been added to UFT or used to modify it. For periods of time between 14 to 28 days, UFT was administered twice daily. Oral UFT's effectiveness in treatment of large-bowel cancer has resulted in objective responses of about 40% when paired by oral LV (50 mg/dose)[122].When UFT was given alone or in conjunction with lower dosages of LV, responding rates varying from about 25% (range, 17% to 39%) occurred. The 28-day dosing schedules result in the greatest amount intensities for UFT. When combined with oral LV 150 mg per day, the maximum tolerated dose (MTD) for UFT under this dosing regimen is 300 mg/m^2 per day. Diarrhoea has historically been a dose-limiting toxicology (DLT) of UFT. The frequent mentions of exhaustion, stomatitis, nausea, and throwing up are also toxicities[123].

4.27. Histrelin

Histrelin acetate (hence referred to as histrelin) is only a long-lasting synthetically produced luteinizing hormone-releasing hormone (LHRH) agonist analogue available as a once-yearly subcutaneous implant (Vantas) that is advised for the palliative therapy of advanced PCa. In terms of pharmacology, it is the most potent luteinizing hormone-releasing hormone (LHRH) activator currently available[124].The cylindrical implant's 50 mg inner core of histrelin is encircled by a tolerant and non-biodegradable hydrogel reservoir, which allows for passive diffusion to release histrelin continuously at an average rate of 50 mg per day for a year. The implant itself is cylindrical & has a diameter of 3 mm and a length of 3.5 cm. The implant is easily placed superficially into the

inner aspects of the highest non-dominant arm utilising a specifically designed implantation instrument[125].



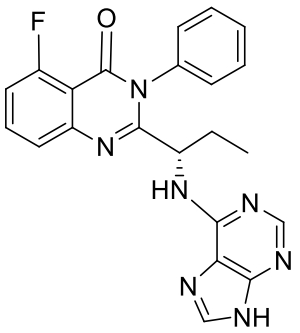
Histrelin (220810-26-4)

27

4.28. Idelalisib

Phosphoinositide 3-kinase delta (PI3Kδ) inhibitor idelalisib, also identified as GS-1101, CAL101, IC489666, and Zydelig, has recently received approval to treat a few haematological malignancies[126].Based on the findings from the Phase I trial and its pharmacokinetic properties, 150 mg of idelalisib administered via mouth every 12 hours is the suggested dose[127]. A reduced intake of 100 mg twice a day is indicated, if clinically necessary. The elimination half-life is 8.2 hours. Despite not being clinically relevant, eating extended the time until peak plasma concentration between 2 to 4 hours[128].

Aldehyde oxidase (AO) and cytochrome P450 3A (CYP3A) are principally responsible for transforming it into the inactive metabolite GS-563117. Idelalisib plasma levels may be impacted by interactions of drugs involving CYP3A inducers and/or inhibitors, however since AO is the predominant metabolising enzyme, these interactions may not have a clinically significant effect. Idelalisib and the metabolite it produces, GS-563117, have high protein binding levels of 94% as well as 99%, respectively. 78% of the medication is excreted mostly through the liver and bile, while just 15% is excreted through the urine. In renal impairment, dosage modification is unnecessary due to the limited urine excretion [129].



Idelalisib (870281-82-6)

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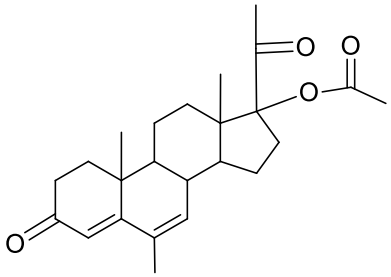


Megestrol acetate (595-33-5)

29

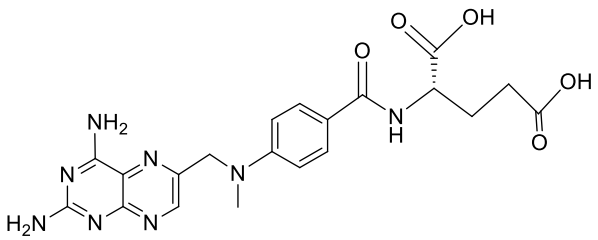
4.29. Megestrol acetate

The most effective progesterone derivative for oral use is megestrol acetate which has greater gastrointestinal absorption and bioavailability. Breast cancer patients frequently receive hormonal treatments[130]. Megestrol acetate is widely utilised as a second-line treatment for hormonal disorders, with doses ranging from 160-1,600 mg/day, to treat advanced breast cancer. Higher doses are thought to be linked to more frequent and severe negative effects, involving 20% to 50% of people reporting an increase in hunger and weight gain. Edoema, breathing difficulties hypertension, loose stool, and fatigue are minor adverse effects when taking high doses[131].

4.30. Methotrexate

Methotrexate (MTX), formerly known as amethopterin, is an antifolate that also has anticancer and immune-suppressive properties. MTX is employed for treating psoriasis, rheumatoid arthritis, & abortion in besides cancer [132].It is difficult to distribute MTX to the central nervous system (CNS), especially when treating brain tumours, non-Hodgkin lymphomas, and acute lymphoblastic leukaemia[133].Acute lymphoblastic leukaemia patients get systemic

and intrathecal administration of MTX to avoid CNS recurrences. One of the few licenced cancer drugs, MTX, needs regular plasma level monitoring to avoid toxicities. This substance's plasma half-life ($t_{1/2}$) ranges from two to ten hours. A more accurate forecast of the MTX plasma level over time is made by administration by intravenous[134].A better bioavailability results from administering smaller dosages (42% for dose 40 mg/m^2). Lower bioavailability is associated with larger doses (18% for doses>40 mg/m^2). The therapeutic and dangerous plasma concentrations of MTX vary depending on the dose given. After 24 hours, a larger concentration is seen after administering of a higher dose[135].

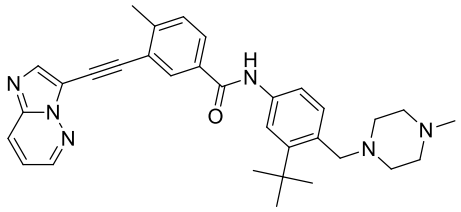


Metothrexate (59-05-2)

30

4.31. Ponatinib

3rd generation Tyrosine kinase inhibitor (TKI) ponatinib is now authorised for therapy of CML [136]and Ph+ ALL individuals who have experienced treatment failure with second-generation TKIs when used as prescribed [137]. Since their introduction, 108TKIs have altered the landscape of treatment for hematologic malignancies, which involves acute lymphoblastic leukaemia (ALL) [138]as well as chronic myeloid leukaemia (CML).Ponatinib's recommended beginning dose is 45 mg once daily[139].



Ponatinib (943319-70-8)

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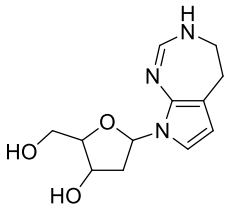


Pentostatin (53910-25-1)

32

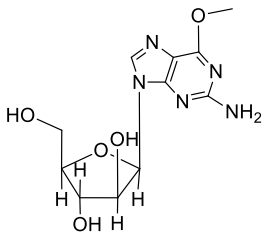
4.32. Pentostatin

The most effective inhibitor of adenosine deaminase (ADA) is pentostatin (2'-deoxyco-formycin). The therapeutic effectiveness of adenosine nucleoside antibiotics is improved by this naturally occurring antibiotic as well as utilised for treating a variety of lympho-proliferative illnesses such as T-cell lymphoma and B-cell chronic lymphocytic leukaemia as well as cutaneous T-cell lymphoma [140]. This function by preventing the deamination of adenosine analogs such as ara-A, cordycepin, formycin, and others. Pentostatin is used to treat some haematological malignancies because it selectively kills lymphocytes or specifically impairs healthy immune function without causing cellular lysis[141].A relatively small amount of 4 mg/m^2 administered at periods of one to two weeks which was utilised for treating numerous types of advanced B cell malignancies. At this dosage, patients typically tolerate the medication well and there are no significant side effects [142].145 patients with post-thymic T-cell malignancies received via vein DCF (2'deoxycoformycin/pentostatin) at a dosage of 4 mg/m^2/week during the first 4 weeks, subsequently every 2 weeks till a peak response; the final 30 patients had injections every week until a maximal response[143].

4.33. Nelarabine

The therapeutic agent nelarabine (compound 506U78; Arranon) is demethylated by adenosine deaminase and yields the deoxyguanosine analogue 9-b-D-arabinofuranosylguanine (ara-G). Deoxyguanosine's cytotoxic effects on T lymphoblasts are extremely subtle. The T-cell

response to nelarabine is due to the build-up of deoxyguanosine triphosphate and subsequent repression of ribonucleotide reductase, DNA synthesis, with ultimately the breakdown of cells [144].For adults, 40 mg/kg/day were the highest dose that could be handled, while for children, it was 60 mg/kg/day, given over a 5-day period. Dose-limiting neurotoxicity signs included drowsiness, brain damage, epileptic fits altered mental status, obtundation, and progressive paralysis[145].



Nelarabine (121032-29-9)

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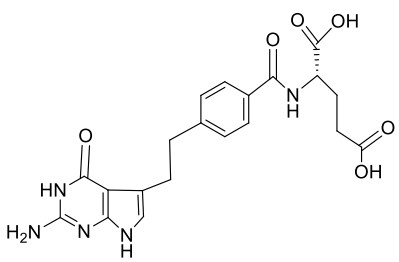


Pemetrexed (137281-23-3)

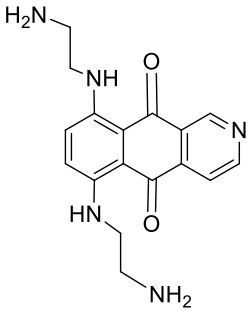
34

4.34. Pemetrexed

Pemetrexed is a special antifolate that relies on pyrrolo[2,3-d] pyrimidines. Several folate-dependent enzymes thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyl transferase, and aminoimidazole carboxamide ribonucleotide formyl transferaseis among those that pemetrexed inhibits[146]. Pemetrexed has a mild toxicity pattern when used solely yet at a dosage of 500 mg/m^2 given as a 10-minute administration one time over 21 days, both dose-limiting and myelosuppressive effects are evident[147].

4.35. Pixantrone dimaleate

Pixantrone attaches to DNA strongly through covalent bonding due to its distinctive chemical structure having two amino groups, with the guanine base producing an N—C—N bridge. Due to its new way of action, it has less ability to produce the heart toxicity-causing species of reactive oxygen, binds iron, and generate alcohol metabolites[148]. Furthermore, it has been shown that the formation of covalent pixantrone-DNA adducts is enhanced by CpG methylation, which is exclusive to tumour cells. Pixantrone facilitates the interaction from the DNA main groove, according to studies. Yet, there was also evidence of a modest groove connection. The production of covalent adducts at guanine N-2 sites, which are hypothesized to contribute to Pixantrone's anticancer activity, is supported by the minor groove association[149].An 85 mg/m^2 dose of pixantrone dimaleate, which is equal to 50 mg/m^2 of pixantrone base, was used in clinical trials. On the days 1, 8, and 15 of a cycle lasting 28 days, an amount of 50 mg/m^2 (based on BSA) is advised to be administered intravenously throughout as many as six cycles. Every cycle should start with a weight check. Following reconstitution along with Sodium chloride, 0.9 percent, in 5 ml and subsequent dilution by sodium chloride solution (0.9%) 250 ml as the final dosage, pixantrone is delivered intravenously[150].



Pixantrone Dimaleate (144675-97-8)

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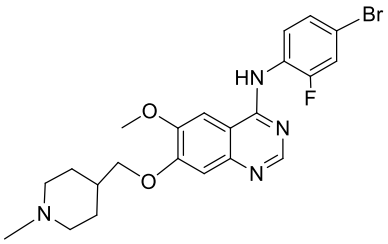


Vandetanib (443913-73-3)

36

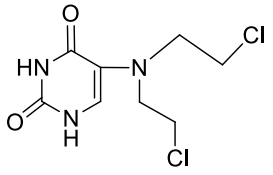
4.36. Vandetanib

The proto-oncogene c-Ret, the vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 and VEGFR-3), and, at higher dosages, epidermal growth factor receptor (EGFR), are all targets of the drug vandetanib [151]. It stops auto phosphorylation and inhibits proto-oncogene c-Ret kinase function by attaching to the adenosine triphosphate binding location of the enzyme. It was initially developed as an effective EGFR, or epidermal growth factor receptor[152].The first drug to show effectiveness

in treating persons with metastatic or locally advanced MTC was vandetanib. In a phase I trial, doses of as much as 300 mg per day proved well-tolerated in 77 individuals who had solid carcinomas other than thyroid cancer, with diarrhoea, hypertension, and skin rash being the most common dose-limiting side effects. In phase II study in familial MTC which began at 100 mg per day revealed similar results[153].

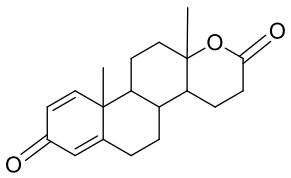
4.37. Uracil mustard

Minor quantities of uracil mustard are notably effective for the medical management of chronic myeloid leukaemia as well as chronic lymphatic leukaemia, in addition to maintenance; it swiftly decreases the measurement of the spleen, liver, and lymph nodes that recovers normal white blood cell counts. Although it will not help cure acute leukaemia, uracil mustard will lower the overall number of white blood cells in patients with high counts[154]. Uracil mustard was administered orally to the patients, typically beginning with an initial dosage of 3-5 mg everyday by oral tradition, administered in singled as well as split doses after meals. Depending on the patients' clinical and haematological response, the amount given was then reduced to 1 mg at least once per week, then to 1-3 mg daily. Numerous of these patients received outpatient care because they did not need to be hospitalised over this purpose[155].



Uracil Mustard (66-75-1)

37



Testolactone (968-93-4)

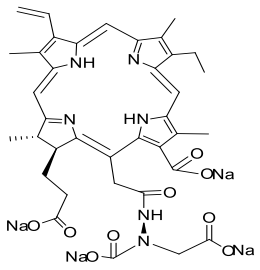
38

4.38. Testolactone

Testolactone, a constituent of the first kind of aromatase inhibitors that resembles testosterone structurally. The first steroids used to treat metastatic breast cancer were non-specific irreversible aromatase inhibitors. Its primary method of action was the inhibition of estrogen synthesis, which was used to treat conditions such as familial male-limited premature puberty, Mc Cune-Albright syndrome, excess sex steroid disorders, and estrogen-dependent breast cancer, etc[156].Testolactone loses all the biological characteristics of its parent testosterone, including virilization, when a double bond between the first and second carbon atoms is introduced. It is most effective when taken orally in doses of 1 gm daily[157].

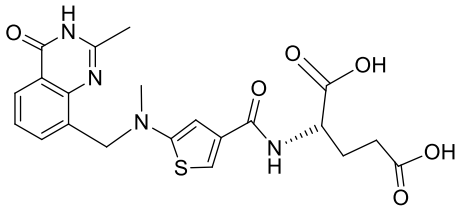
4.39. Talaporfin sodium

Talaporfin sodium with a diode laser has been used successfully in PDT (photodynamic therapy) to treat local failure chemotherapy or radiation therapy (CRT) in oesophageal carcinoma.A sensitizer chemical that is used in PDT therapy preferentially gathers in neoplastic lesions and, when activated by light, causes cell death [158].The administration of Photofrin through a vein at a dosage of 2 mg/kg is the initial step in PDT procedures using porfimer sodium [159]. Then, 48–72 hours after taking the medication, laser therapy employing the 630 nm excimer dye laser is carried out[160]. A microlamsfibre is used to send the excimer dye laser through the endoscope's operational channel which has been set in front of the lesions[161]. Porfimer sodium-based first-generation PDT treating oesophageal cancer has some drawbacks, including the requirement for such a highly-priced excimer dye laser equipment and a lengthy sun-shade period of roughly 6 weeks to prevent the danger of skin phototoxicity[162],[163].



Talaporfin Sodium (220201-34-3)

39



Ratitrexed (112887-68-0)

40

4.40. Raltitrexed

Raltitrexed belongs to the antimetabolite class of cytotoxic medications. It inhibits thymidylate synthase[164]. The RALTRIXED-based chemo-therapy doublet is an efficient, secure, and simple

to administer treatment combination for metastatic advanced colorectal cancerpatients with cardiac comorbidities, dihydropyrimidine dehydrogenase deficiency, or central line treatment who require a standard polychemo-therapy doublet but cannot receive 5-FU (5-fluorouracil)[165].439 patients without treatment of CRC were randomly randomised to get both raltitrexed at a dosage of 3 mg/m2 every twenty-one days and the Mayo Clinic protocol of 5-FU + folinic acid for the first phase III trial that revealed clinical findings[166]. Grade three and four toxicities, that include leukopenia, diarrhoea, and mucositis, were much less common in 135 patients who received raltitrexed, and they also required less hospitalisation time for medication delivery[167].These all-drugs work by interfering with the growth and division of cancer cells, thereby slowing down or stopping their progress-sion. These are numerous anti-cancer drugs available, each with its own mechanism of action and target specific types of cancer along with their clinical trials. To provide comprehensive overview, we have compiled a list of commonly used anti-cancer drugs along with their respective drug class and indications. The table below presents the information in a concise and organised format for easy reference.

S. No.	Drug Name	Drug Class	Indications	Mode of Action	Dosage	Reference
1.	Abarelix	Gonadotropin-releasing hormone (GnRH) antagonists	Advanced as well as symptomatic prostate cancer	Suppression of the production and release of gonadotropin-releasing hormone (GnRH)	50 mg/day	[41]–[44]
2.	Abiraterone	Androgen biosynthesis inhibitors	Advanced prostate cancer	Inhibition of androgen synthesis via targeting production of testosterone	1 g/day	[45]–[47]
3.	Cladribine	Purine analogues or nucleoside metabolic inhibitors	Certain types of leukemia, such as hairy cell leukemia, chronic lymphocytic leukemia (CLL)	Interfering with DNA synthesis and repair processes within cancer cells	0.1 mg/day	[48]–[50]
4.	Carmofur	Antimetabolites or pyrimidine analogues	Gastrointestinal cancer	Inhibition of dihydropyrimidine dehydrogenase (DPD) enzyme and modulation of the immune response	0-1 g/ ml of HCFC	[51]–[54]
5.	Axitinib	Tyrosine kinase inhibitors (TKIs)	Advanced renal cell carcinoma (kidney cancer)	Inhibition of vascular endothelial growth factor (VEGF) receptors	5 mg/day	[55]–[58]
6.	Bosutinib	Tyrosinr kinase inhibitors (TKIs)	Chronic myeloid leukemia (CML)	Inhibits Bcr-Abl, Src family kinase (Src, Lyn, Hck), and other receptor tyrosine kinases	200-800 mg/day	[59]–[61]
7.	Cabozantinib	Tyrosine kinase inhibitors (TKIs)	Advanced hepatocellular carcinoma, thyroid cancer, lung cancer, prostate cancer, advanced renal cell carcinoma	Inhibition of various tyrosine kinase receptors, such as vascular endothelial growth factor receptor (VEGFR), MET (hepatocyte growth factor receptor), RET (rearranged during transfection), AXL	40-140 mg/day	[62], [63]
8.	Afatinib	Tyrosine kinase inhibitors (TKIs)	Non-small cell lung cancer (NSCLC)	Inhibition of epidermal growth factor receptor (EGFR)	40-50 mg/day	[64], [65]
9.	Capecitabine	Antimrtabolites or fluoropyrimidine analogues	Breast cancer, colorectal cancer, gastric cancer	Converts into its active form, 5-fluorouracil and leading to inhibition growth and replication of cancer cell	1657 mg/day	[66]–[68]
10.	Azacitidine	Nucleoside metabolic inhibitors or hypomethylating	Blood cancers, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)	Converts into its active metabolite, 5-azacytidine and Leading to inhibition of DNA and RNA synthesis	75 mg/day	[69]–[71]
11.	5-Fluorouracil	Antimetabolites or fluoropyrimidine analogues	Colorectal cancer, breast cancer, skin cancer[80]	Inhibition of Thymidylate Synthase (TS) and inhibition of RNA processing	400 mg/day	[72]–[74]
12.	Eribulin	Microtubule inhibitors or tubulin polymerization inhibitors	Advanced or metastatic breast cancer	Inhibiting of dynamic assembly and disassembly of microtubules	<0.1-1 mg/day	[75]–[77]
13.	Degarelix	Gonadotropin-releasing hormone (GnRH) antagonists	Advanced prostate cancer	Inhibition of GnRH receptor in the pituitary gland	635 mg/day	[78]–[81]
14.	Decitabine	Nucleoside metabolic inhibitors or hypomethylating	Myelodysplastic syndromes (MDS), acute myeloid leukemia (AML)	DNA methyltransferase inhibitor	5 mg/day	[82], [83]
15.	Cytarabine	Antimetabolites or pyrimidine analogues	Acute myeloid leukemia (AML), acute lymphoblsticleukemia	Interfering with replication and repair processes of cancer cells, inhibition of DNA polymerase	100-400 mg/day; 2000-3000 mg/day	[84]–[87]

			(ALL), hematological malignancies			
16.	Fludarabine	Antimetabolites or purine analogues	Chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphomas, acute lymphoblastic leukemia (ALL)	Inhibition of DNA and RNA synthesis, including apoptosis, and modulating immune response	25 mg/day; 40 mg/day	[88], [89]
17.	Arabinoside cytosine	Antimetabolites or pyrimidine analogues	Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), hematological malignancies	Inhibition of DNA polymerase	30-50 mg/day	[90]–[92]
18.	Dabrafenib	BRAF protein kinase inhibitors	Advanced or metastatic melanoma	Inhibition of BRAF protein	2.5 mg/day; 25 mg/day	[93], [94]
19.	Dexamethasone	Corticosteroids or glucocorticoids	Anti-inflammatory and immunosuppressive	Interaction to Glucocorticoid receptors (GR)	20 mg/day	[95]–[97]
20.	Doxifluridine	Antimetabolites or fluoropyrimidine analogues	Anti-neoplastic age[110]nt	Inhibit DNA synthesis and cell division as well as inhibition of thymidylate synthase	4 g/day	[98]–[101]
21.	Trastuzumab emtansine	Antibody-drug conjugates (ADCs) or monoclonal antibodies, HER_2/neu receptor antagonist	HER2- positive breast cancer	Internalization and lysosomal degradation	3.6 mg/day	[102]–[106]
22.	Mercaptopurine	Antimetabolites or purine analogues	Acute lymphoblastic leukemia (ALL)	Interference with DNA synthesis and cell devision	20-70 mg/day	[107]–[110]
23.	Leucovorin	Folic acid analogues or folate derivatives		Interferes with DNA synthesis and cellular functions	15-30 mg/day	[111]–[113]
24.	Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitors	Chronic lymphocytic leukemia (CLL), mentle cell lymphoma (MCL), Waldenstrom macroglobulinemia (WM)	Bruton's tyrosine kinase (BTK) inhibitor, interleukin-2-inducible T-cell kinase (ITC)	420 mg/day	[114]–[117]
25.	Gemcitabine	Antimetabolites or nucleoside analogues	Pancreatic cancer, non-small cell lung cancer, bladder cancer	Inhibit DNA synthesis and cell division as well as inhibition of ribonucleotide reductase	70 mg/day	[118]–[120]
26.	Ftorafur	Antimetabolites or fluoropyrimidine analogues	Colorectal cancer, gastric cancer, breast cancer, pancreatic cancer	Inhibition of thymidylate synthase, disruption of RNA processing as well as DNA repair	150-300 mg/day	[121]–[123]
27.	Histrelin	Gonadotropin-releasing hormone (GnRH) agonists	Puberty, prostate cancer, and endometriosis	Gonadotropin-releasing hormone (GnRH) agonists	50 mg/day	[124], [125]
28.	Idelalisib	Phosphoinositide 3-kinase (PI3K) inhibitors	Chronic lymphocytic leukemia (CLL) and follicular lymphoma	Inhibitor of enzyme phosphatidylinositol 3-kinase (PL3K) delta	100-150 mg/day	[126]–[129]
29.	Megestrol acetate	Progestins or synthetic progesterone derivatives	Breast and endometrial cancer as well as advanced or metastatic cancer	Progestin receptor activation, suppression of gonadotropin secretion	160-1600 mg/day	[130], [131]
30.	Methotrexate	Antimetabolites or folate antagonists	Leukemia, lymphoma, and solid tumours	Inhibition of dihydrofolate reductase (DHFR)	40 mg/day	[132]–[135]
31.	Ponatinib	Tyrosine kinase inhibitors (TKIs), specially BCR-ABL inhibitor	Chronic myeloid leukemia (CML) as well as Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)	Overcome specific resistance mutations such as T315L mutation	45 mg/day	[136]–[139]
32.	Pentostatin	Antimetabolites or purine analogues	Hairycellleukemia	Inhibition of adenosine deaminase as well as disruption of DNA synthesis	4 mg/day	[140]–[143]
33.	Nelarabine	Antimetabolites or purine analogues	T-cell acute lymphoblastic leukemia (T-ALL) as well as T-cell lymphoblastic lymphoma (T-LBL)	Conversion of active metabolite ara-G, incorporation of ara-G into DNA, inhibition of DNA synthesis, induction of apoptosis and lymphoblast-specific action	40-60 mg/day	[144], [145]
34.	Pemetrexed	Antimetabolites or folate antagonists	Non-small cell lung cancer, mesothelioma	Inhibition of folate metabolism as well as disruption of cell division	500 mg/day	[146], [147]
35.	Pixantrone dimaleate	Anthracenediones or DNA intercalators	Relapsed or refractory aggressive non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL)	Topoisomerase II inhibition, DNA intercalation	85 mg/day	[148]–[150]
36.	Vandetanib	Tyrosine kinase inhibitors (TKIs)	Medullary thyroid cancer and non-small	Inhibition of angiogenesis as well as inhibition of	100 mg/day	[151]–[153]

			cell lung cancer	receptor tyrosine kinases, such as EGFR, VEGFR, RET		
37.	Uracil mustard	Alkylating agents or nitrogen mustard derivatives	Colorectal cancer, breast cancer, ovarian cancer, lung cancer	Inhibition of thymidylate synthase	1-3 mg/day	[154], [155]
38.	Testolactone	Aromatase inhibitors	Advanced breast cancer in postmenopausal women	Aromatase inhibition, estrogen receptor modulation	1 g/day	[156], [157]
39.	Talaporfin sodium	Photosensitizing agent or photosensitizers	Skin cancer, lung cancer	Selective accumulation in tumour tissue, subsequent destruction of tumour cells	2mg/day	[158]–[163]
40.	Raltitrexed	Antimetabolites or folate antagonists	Colorectal cancer	Inhibition of thymidylate synthase, disruption of folate metabolism, induction of cell cycle arrest, and induction of apoptosis	3 mg/day	[164]–[167]

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