
Section B: Organic, Analytical and Pharmaceutical Chemistry.

Review Article

Off-Label Drug Use: Literature review article

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Abstract

The term off-label drug use (OLDU) has been used extensively during the last decades in medical literature. Although, there are many health care professionals who are under appreciation of this term which is used enormously in the medical field especially in case of resistant or idiopathic, orphan, diseases. The most usual form of OLDU involves prescribing of a current, available medication for a certain condition (disease or symptoms) that has no FDA approval. There is a significant difference between on-label drug use and off-label drug use which will be summarized in the form of that on-label drug use is FDA approved on its use, dose, route of administration, certain age, and certain conditions. On the other hand, off label drug use is legal, marketed, prescribed but not FDA approved. The use of off-label drug use is about 21% with an increased rate lately. There are many different classes that have off-label drug, un-approved use. Herein, we will spot on the main classes and the common drugs that are used for this purpose. The top classes that have an off-label drug use are cardiac therapies, anti-convulsant, anti-asthmatics, allergy therapies, psychiatric therapy, peptic ulcer, dyspepsia therapy, anti-microbial, anti-hypertensive, and women's health therapy, respectively. The widest era that uses this term is the western world. Main people effected to this use are pediatrics, oncology, critical care, and pregnancy, respectively. After usage of the drug as an off label, the owner company must apply different clinical phases to approve this drug for this purpose with respect to other quality control tests such as stability test. This means that the drug is still under investigation until the FDA approves it. The demerits that lead us not to be sure to use the off-label drug are reimbursement (the insurance company will not pay again for another use to be approved from the authority), thus, it will get more profits, high risk of an adverse effect that will appear by serendipity and no insurance on the biological activity that will get. The decision of using off-label drug is different from one to another with total respect to the users according to the history and background. Without any doubt, OLDU has become a life saver for many patients and many disasters that appear like those of COVID-19 pandemic and cancer patients. The collection of those uses is up to 2024.

1. Introduction

Off-label drug use (OLDU) is a quite common clinical practice worldwide. Off-label use of drugs refers to the practice of prescribing medications for an unapproved disease, condition, or in a manner that not approved by the regulatory authorities. This practice varies significantly from country to country due to differences in legal and regulatory frameworks [1]. Recently, it has shown that there are many diseases, such as cancer, or emergent COVID-19, has non-specified treatment. This led us to focus on another use of the old drug that has an efficient action on this disease. There are many diseases cured or responded to an old drug such as cancer, pulmonary disorders, urinary incontinence, sexual disorder, spinal cord injury, weight loss, anti-emetic, anti-viral, nightmares, obsessive compulsive disorder, pericarditis, and schizophrenia. This new use is shown after making a drug repurposing, ret asking, reprofiling, therapeutic switching which is very widely used in recent times. The clinical studies, it was found that an old drug is used for a new purpose, but not FDA approved and this simply enumerate the term of off-label drug use. Thus, the owner company of the active constituent will make a clinical trial to this drug to be approved. Another important point in term of OLDU is if there are any change of the age (drugs prescribed outside approved age range) , dose (drugs given at doses other than the stated in the pamphlet) , use (drugs used for indications other than the prescribed one) , route of administration (drugs that taken with different route of administration rather than those mentioned in the pamphlet) [2]. The use of OLDU is quite common worldwide, about 21% while in case of cardiac therapy and anti-convulsant reaches about 46% [3]. Studies have shown that an outsized proportion of prescriptions fall into this category. In 2003 reports found that approximately 21% of prescriptions for the leading drugs in various classes were off label. The most common percentage from the top 15 drug classes found on cardiac therapy, anticonvulsants, antipsychotics, and antibiotics had the highest rates of off-label use. Unfortunately, many off-label uses lack strong scientific evidence. Around 73% of off-label drug uses were found to have little or no support [4]. The most common affected patients by the help of off label drug use are cardiovascular patients, CNS patients, pediatrics, oncology, critical care and pregnant, respectively.

There is a wide difference between on and off-label drug use. The first one is the approved drug from FDA on its use, dose, route of administration, age and therapeutic target, so, it is described to be legal, approved, safe and effective. After its approval from the regulatory authority, the owner company will make a specified package insert, physician labelling format, which give a tight information and instruction about the drug dosage form, name of the active constituent, strength, contraindication, therapeutic profile, side effects, route of administration, specific criteria that deal with, boxed warning, limitation statement and precaution. On the other hand, off-label drug use is a new therapeutic use of the drug but without an approval from the authority [5]. It is used in the case of resistant diseases such as cancer or the new emergent cases that appear such as COVID-19 and the use of different antibiotics, anti-viral, anti-malarial and anti-scabies. Also, orphan diseases, idiopathic, that have unknown mechanism or mode of action. Off-label drug use should have different clinical phases, safety, and efficacy tests to be approved. Although off-label use can provide benefits, it also poses risks. Patients may experience adverse effects or miss effective treatments. Balancing the potential

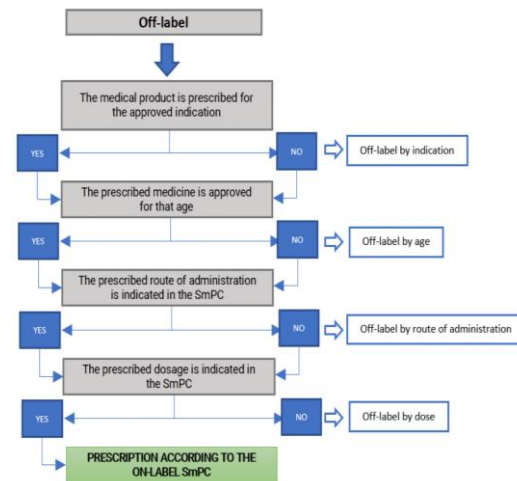


Figure 1: diagram of what is off-label drug.

benefits and risks requires careful assessment by healthcare professionals.

Spotting on the most important classes in the medical and pharmaceutical field. We will discuss the use of off-label drug on the most famous 4 diseases used worldwide. They are anti-cancer, central nervous system agents, cardiovascular drugs and anti-microbial, respectively, in addition to other group that have different classes with different uses.

1. Anti-cancer: -

Cancer is the second-leading cause of death in the United States overall and the leading cause among people younger than 85 years [6]. As is known, cancer is the most challenging disease worldwide nowadays. Cancer cells have a huge proliferation and metastatic characteristics. Cancer is indeed a complex disease that can affect various parts of the body.. Normally, cells grow, divide, and replace old or damaged cells in a controlled manner, apoptosis. When this process goes awry, abnormal cells can proliferate uncontrollably this called tumor. Tumors are masses of tissue formed by these abnormal cells. The two main types of cancer cells are Benign Tumor that do not invade nearby tissues and are usually not life-threatening. However, they can cause symptoms if they press on surrounding structures and cancerous, malignant, tumors. These invade nearby tissues and can spread to other parts of the body, metastasis, they pose a greater health risk. The most common types of cancer are solid tumors (e.g., breast, lung, colon) arise from specific tissues. Blood cancers (e.g., leukemia, lymphoma) affect blood-forming cells and do not form solid tumors [7]. we will mention some types of resistant cancer that do not respond effectively to monotherapy. Certainly! Off-label drug use is a widespread practice in oncology. Half of the chemotherapy drugs administered are used for conditions not specifically listed on the FDA-approved drug label. In fact, the National Cancer Institute (NCI) acknowledges that the standard of care for certain types or stages of cancer often involves the off-label use of one or more drugs. This approach allows oncologists to explore alternative treatment options and tailor therapies to individual patient needs. References contain mechanism of action. Drugs are classified according to their on-label use.

Table I. Difference between on and off-label drug use.

	On-label drug	Off-label drug
Approval	Approved	Un-approved
Authority	Legal to be use	Legal but not regulated
Marketing	Can be marketed	Not legal to be marketed
Limitation	Has a specified drug label	Non specified drug label
Adverse effect	No adverse effect unless mentioned	Big chance to have an adverse effect
Clinical trials	Enter all phases of clinical trial	Not complete clinical phases yet
Therapeutic evidence	Proven biological activity	Expected biological activity

2. Cardiac therapy: -

The cardiovascular system, also referred to, circulatory system, pumps, and filters blood throughout the body. The heart, blood, and arteries, all work together to supply blood for the body's cells. Blood carries carbon dioxide to the lungs for expiration and picks up oxygen via a network of arteries, veins, and capillaries. The blood transports nutrients from the small intestine to all cells. Off-label use refers to the practice of prescribing a drug for a purpose other than its FDA-approved indication. Here are some main points about cardiac agents and their off-label use in different eras of cardiovascular system, respectively. Arterial hypertension, Heart disease, Arrhythmias, Hyperthyroidism, Migraine prophylaxis and sexual performance. Remember that while off-label use can provide benefits, it is essential to weigh the risks and benefits carefully, especially when strong scientific evidence is lacking. Always consult with a healthcare professional before using any medication off-label [24]. We will mention the most common ligands used as OLDU in treatment or mitigation of cardiovascular patients below, Table 3. References contain mechanism of action. Drugs are classified according to their on-label use.

3. Central nervous system: -

The central nervous system is the supreme command center of the body. It receives, analyzes, integrates, processes, and generates neural impulses that control all the body functions. It consists of the brain and spinal cord. The causative agents that precipitate central nervous system diseases are the imbalance in hormones and neurotransmitters which lead to depression, convulsion, psychosis, attention defect hyperactivity disorder, ADHD, nightmares, sleep disturbance, Alzheimer, obsessive compulsive disorder and many other diseases. With the help of OLDU, it was found that many symptoms and conditions are mitigated by prescribing OLDU. The quite type of OLDU in CNS is the anti-convulsant. The main merit of OLDU in treatment of CNS problems is the control on the internal environment but remember that control of the internal hormones and neurotransmitters is not an easy pathway because if any imbalance occur can lead to severe hazards to the patient health. To be honest and concise even one of

those agents can play a several roles in distinct parts and with different mode of actions as we will mention below. Drugs are classified according to their on-label use.

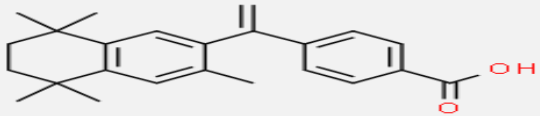
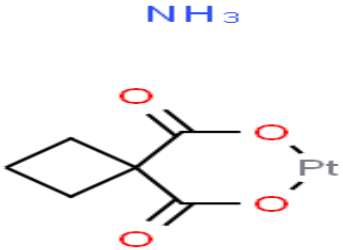
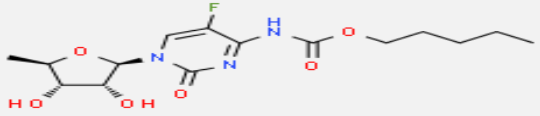
4. Anti-microbial: -

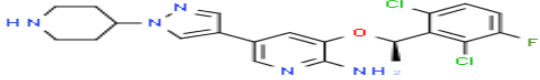
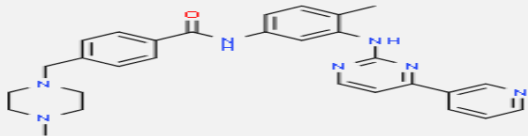
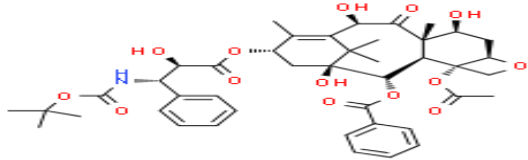

Antimicrobial agents are medications that kill or prevent the growth of living micro-organisms. According to different hot spots in microorganisms (M.O) that can be attacked either the cell wall, protein subunits, cell membrane, leakage of the cell, protein synthesis, genome of the M.O, essential enzymes, and different pathways of M.O life cycle. Thus, too many anti-biotic, anti-septic, anti-fungal and anti-protozoal can function as an OLDU. Antibacterial agents (also known as antibiotics) are used to treat bacterial infections. Antimycobacterial are medicines that are used to cure tuberculosis and other mycobacterial disorders. Antivirals (efficient versus viral infections such influenza, HIV, and herpes). Antifungals (active against fungal infection). Antiparasitic drugs (effective against parasites and malaria etc...) [56]. The use of OLDU is widely in the market due to different mechanisms of action and distinct types of targets either it is not used only in human based medicine also has a gigantic use in veterinary medicine and infection control. With respect to each class of anti-microbial However one class can be function as a threaten for the other prokaryotic and Eukaryotic References contain mechanism of action. Drugs are classified according to their on-label use.

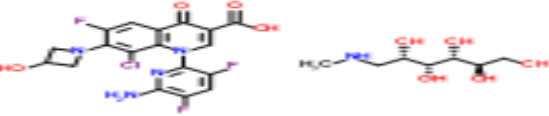
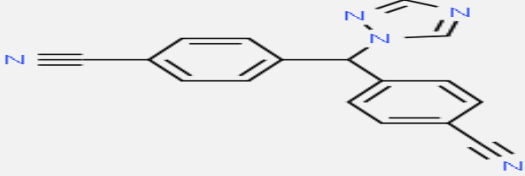
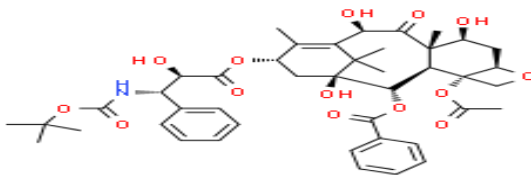
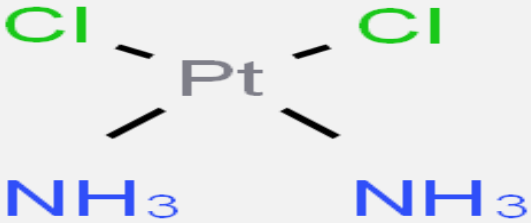
5. Other classes of drugs: -

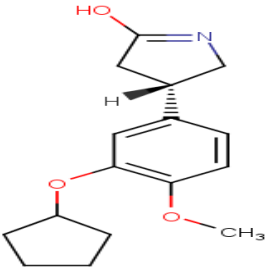
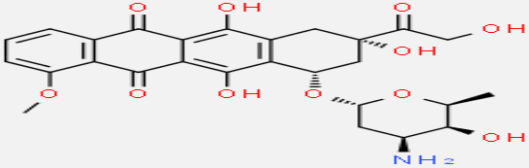
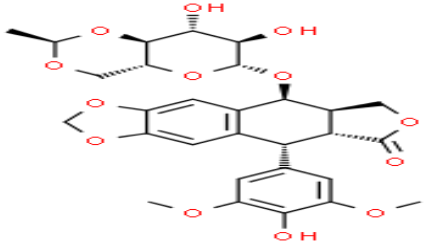
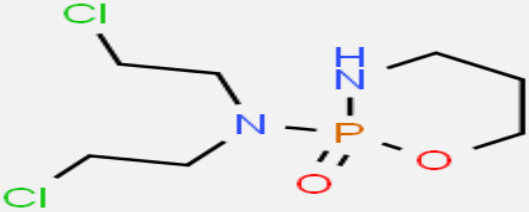
After enumeration of the predominant classes in OLDU we will enumerate a mixture of different classes that are used seriously in the market especially in allergic reaction, sedation, analgesic, genitourinary system, nocturnal enuresis, nausea and vomiting, myalgia, infertility, and reproductive system. The importance of OLDU in those classes has no little importance than those of the most predominant ones but it related to the health care practitioners. As we mentioned before, using OLDU is a risk and benefit decision. References contain mechanism of action. Drugs are classified according to their On-label use.

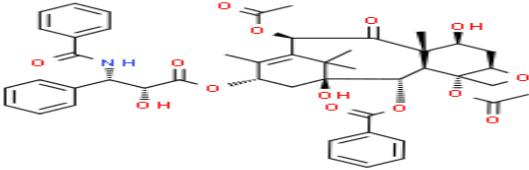
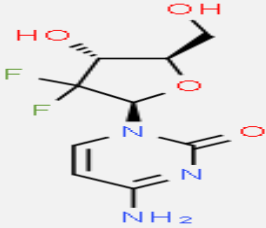
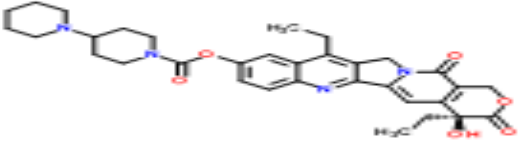
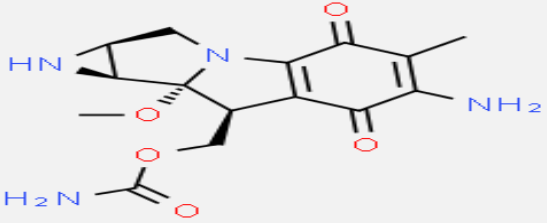
Table 2: Anti-cancer off-label drug use.

No.	Active constituent	Structure	On-label drug use	Off-label drug use	References
1	Bexarotene		Cutaneous T-cell lymphoma	Alzheimer's disease	[8]
2	Carboplatin		Ovarian cancer	Breast, genitourinary, head, neck, thoracic and gynecological	[9]
3	Capecitabine		Anti-metabolite	Gastrointestinal cancer	[10]

4	Crizotinib	 <p>The image shows the chemical structure of Crizotinib, a tyrosine kinase inhibitor. It features a piperidine ring connected to a pyrazole ring, which is further linked to a pyridine ring. The pyridine ring has a chlorine atom and a fluorine atom at the 3 and 4 positions, respectively. The pyrazole ring has a chlorine atom at the 5 position and a methyl group at the 4 position.</p>	Non-small cell lung cancer NSCLC	Acute lymphocytic leukemia ALK	[11]
5	Imatinib	 <p>The image shows the chemical structure of Imatinib, a tyrosine kinase inhibitor. It features a piperazine ring connected to a benzamide group, which is further linked to a pyridine ring. The pyridine ring has a methyl group at the 2 position and a pyrimidine ring at the 4 position.</p>	Chronic myelogenous leukemia	Spinal cord injury	[12]
6	Docetaxel	 <p>The image shows the chemical structure of Docetaxel, a taxane. It features a complex polycyclic core with multiple hydroxyl groups and a side chain containing a phenyl ring and a methyl group.</p>	Multiple metastatic tumor	IV in all solid tumor	[13]
7	Oxaliplatin	 <p>The image shows the chemical structure of Oxaliplatin, a platinum-based anticancer drug. It features a cyclohexane ring with two amino groups at the 1 and 2 positions, and a platinum atom coordinated to two chloride ions and two oxalate ions.</p>	Colorectal cancer	Gastric and pancreatic adenocarcinoma	[10]

8	Fludarabine		Chronic lymphocytic leukemia	Distinct types of leukemia	[14]
9	Letrozole		Breast cancer	Poly cystic ovary syndrome	[15]
10	Docetaxel		Breast cancer, NSCLC, and gastric adenocarcinoma	Ovary, gall bladder, lymphoma, and urinary bladder	[16]
11	Cisplatin		Metastatic testicular tumor, metastatic ovarian cancer, and advanced bladder cancer	Head, neck, gastric and esophagus	[16]

12	Bevacizumab	 <p>The image shows the chemical structure of Bevacizumab, a monoclonal antibody. It features a central benzene ring with a methoxy group (-OCH₃) at the para position and a cyclopentane ring attached via an ether linkage at the other para position. A side chain containing a nitrogen atom and a hydroxyl group is attached to the benzene ring.</p>	Metastatic breast cancer, NSCLC, glioblastoma	Renal carcinoma and ovarian cancer	[16]
13	Doxorubicin	 <p>The image shows the chemical structure of Doxorubicin, a tetracycline antibiotic. It consists of a tetracycline core with a doxorubicin side chain. The side chain includes a glucose moiety and a doxorubicin aglycone moiety, which has a hydroxyl group and a methyl group on the C-13 position.</p>	Leukemia and neuroblastoma	Lymphoma	[17]
14	Etoposide	 <p>The image shows the chemical structure of Etoposide, a topoisomerase II inhibitor. It features a complex polycyclic core with multiple hydroxyl groups and a methyl group. The structure is highly substituted and contains several oxygen atoms in the ring system.</p>	Small cell lung cancer (SCLC)	Lymphoma and Ewing's sarcoma	[16]
15	Cyclophosphamide	 <p>The image shows the chemical structure of Cyclophosphamide, a cytotoxic drug. It consists of a six-membered ring containing one nitrogen atom and one phosphorus atom. The phosphorus atom is double-bonded to an oxygen atom and single-bonded to two nitrogen atoms. One of the nitrogen atoms is bonded to two chlorine atoms, and the other is bonded to one chlorine atom and one hydrogen atom.</p>	Malignant lymphoma , leukemia, retinoblastoma, renal and breast cancer	Ewing's sarcoma, GCT, lymphoma and ovary	[18]

16	Paclitaxel	 <p>The image shows the chemical structure of Paclitaxel, a complex diterpenoid. It features a central taxane ring system with multiple hydroxyl groups, ester side chains, and a phenylisoserine moiety.</p>	Breast and advanced carcinoma of the ovary	Lung, stomach, head, neck, GCT and urinary bladder	[19]
17	Gemcitabine	 <p>The image shows the chemical structure of Gemcitabine, a pyrimidine nucleoside. It consists of a pyrimidine ring with an amino group at the 4-position and a 2-deoxyribose sugar at the 1-position, substituted with two fluorine atoms at the 2-position.</p>	Breast and bladder cancer	Gastrointestinal cancer	[20]
18	Irinotecan	 <p>The image shows the chemical structure of Irinotecan, a topoisomerase II inhibitor. It features a complex polycyclic core with a piperidine ring, a quinoline ring, and a lactone ring, along with various substituents including methyl and hydroxyl groups.</p>	Diverse solid tumor	Gastrointestinal cancer	[20]
19	Mitomycin	 <p>The image shows the chemical structure of Mitomycin, a bicyclic alkaloid. It consists of a bicyclic core with a nitrogen atom, a methyl group, and a side chain containing a methylamino group and a methyl group.</p>	Anal carcinoma	Gastrointestinal cancer	[20]

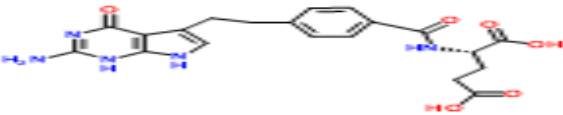
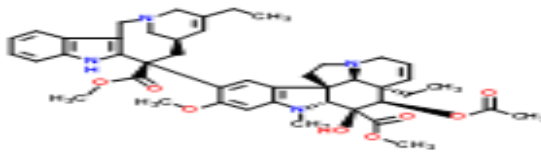
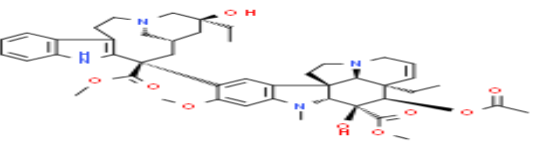
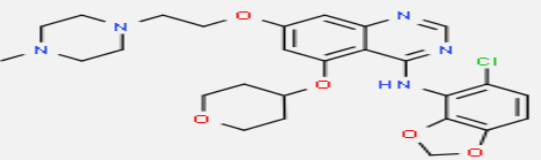
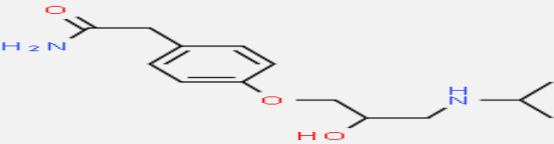
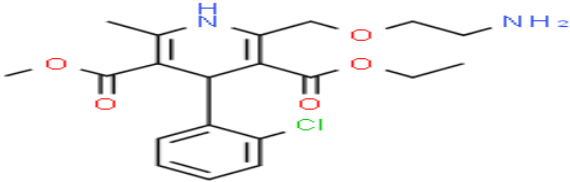
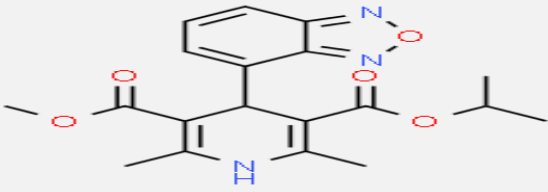
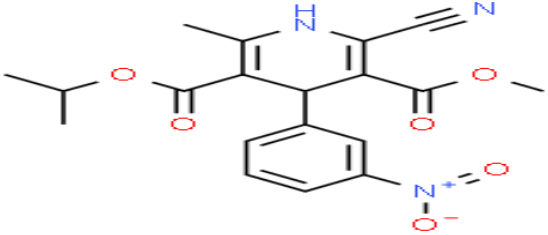
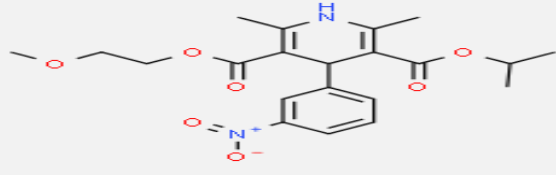
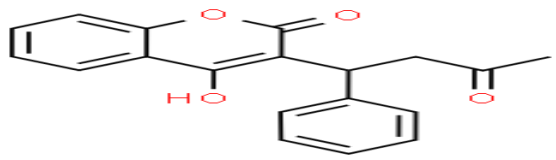
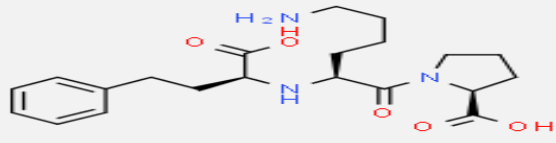
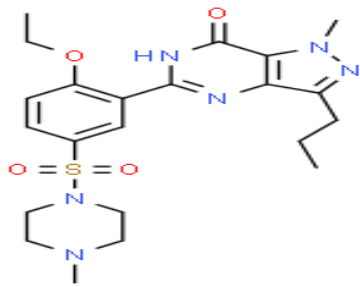
20	Pemetrexed		NSCLC	Thoracic cancer	[20]
21	Vinorelbine		Anti-mitotic	Thoracic cancer and breast cancer	[21]
22	Vinblastine		Hodgkin's, NSCLC, and bladder cancer	Genitourinary cancer and breast cancer cells	[22]
23	Saracatinib		Anti-cancer	Anti-infective (MERS, SARS and Covid)	[23]

Table 3: Cardiovascular agents as an Off -label drugs.

No.	Active constituent	Structure	On-label drug use	Off-label drug use	References
1	Atenolol		Hypertension in adult	Hypertension in children	[25]
2	Amlodipine		Hypertension	Alzheimer's disease	[26]
3	Isradipine		Hypertension	Alzheimer's disease	[26]
4	Nilvadipine		Hypertension	Alzheimer's disease	[26]

5	Nimodipine	 <p>The chemical structure of Nimodipine features a central 1,4-dihydropyridine ring. It is substituted with a 2-(2-ethoxyethyl)acrylate group at the 4-position, a 2-(2-isopropoxyethyl)acrylate group at the 3-position, and a 2-nitrophenyl group at the 2-position.</p>	Hypertension	Alzheimer's disease	[26]
6	Warfarin	 <p>The chemical structure of Warfarin consists of a central coumatin core. It has a 4-hydroxyphenyl group at the 3-position, a 3-oxo-1-phenylbutyl group at the 4-position, and a 4-hydroxyphenyl group at the 5-position.</p>	Oral coagulant anti-	Hypertensive heart diseases	[27]
7	Lisinopril	 <p>The chemical structure of Lisinopril is a proline derivative. It features a 2-phenylpropyl group at the 2-position, a 2-oxo-3-phenylpropyl group at the 3-position, and a 2-oxo-3-phenylpropyl group at the 4-position.</p>	Hypertension	Coronary artery disease, Diabetes Melitus	[28]
8	Sildenafil	 <p>The chemical structure of Sildenafil is a pyrazolo[1,5-a]pyrimidin-6(1H)-one derivative. It has a 4-ethoxyphenyl group at the 7-position, a 2-oxo-3-phenylpropyl group at the 5-position, and a 2-oxo-3-phenylpropyl group at the 6-position.</p>	Pulmonary hypertension	Female sexual disorder	[29]

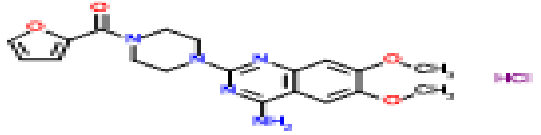
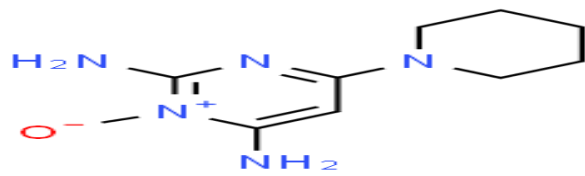
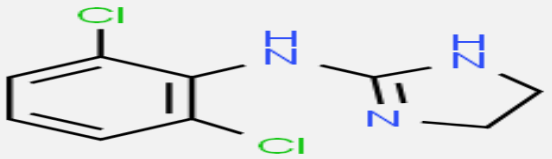
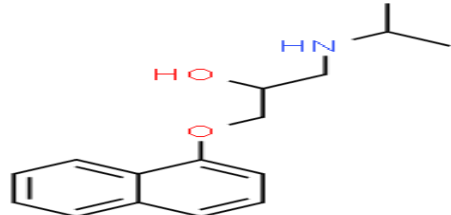
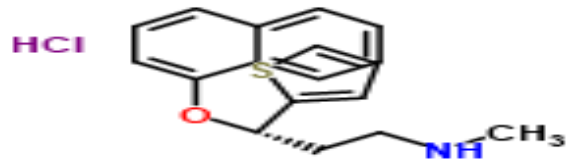
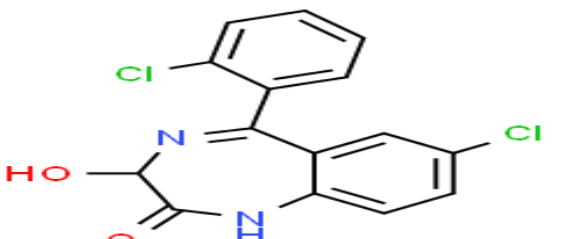
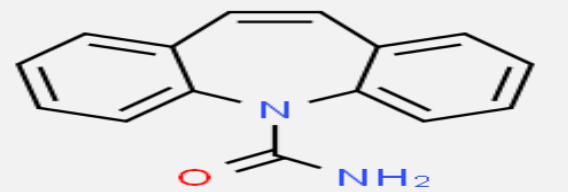
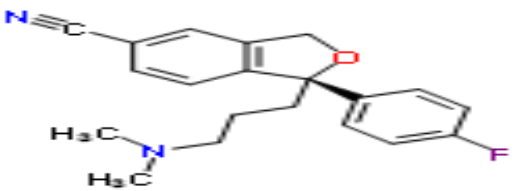
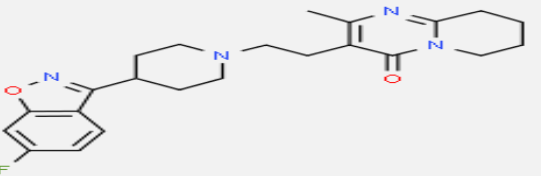
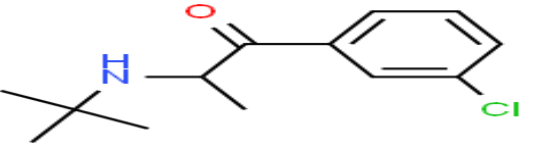
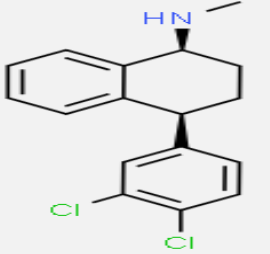
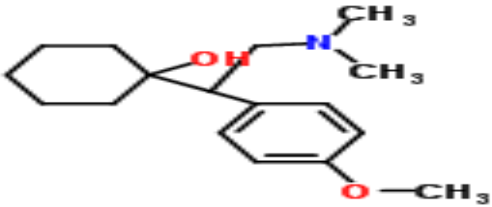
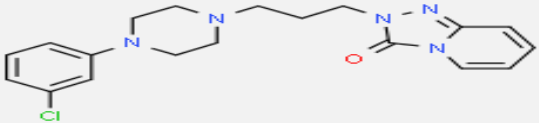
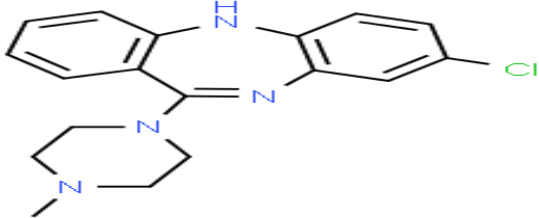
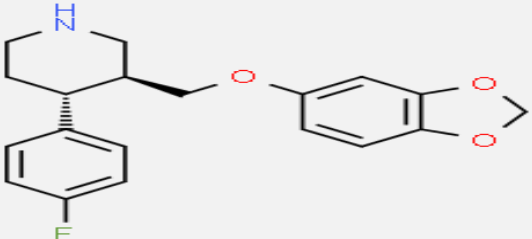
13	Prazosin	 <p>The chemical structure of Prazosin is shown. It features a central benzimidazole ring system. One nitrogen of the benzimidazole is substituted with a propyl chain that ends in a 2,3-dihydro-1H-indolizin-5(1H)-one ring. The other nitrogen of the benzimidazole is substituted with a propyl chain that ends in a 2,3-dihydro-1H-indolizin-5(1H)-one ring. The benzimidazole ring also has an amino group (-NH₂) at the 2-position and a methyl group at the 5-position.</p>	Hypertension	Nightmare related to post-traumatic stress disorder	[31]
14	Minoxidil	 <p>The chemical structure of Minoxidil is shown. It consists of a 1,2,4-triazole ring system. The 1-position of the triazole is substituted with a methylamino group (-NH₂). The 2-position is substituted with a methyl group (-CH₃). The 4-position is substituted with a methyl group (-CH₃). The 5-position is substituted with a propyl chain that ends in a piperidine ring.</p>	Vasodilator	Hair growth	[32]
15	Clonidine	 <p>The chemical structure of Clonidine is shown. It features a benzene ring with two chlorine atoms at the 3 and 4 positions. The benzene ring is substituted at the 1-position with a 2,6-dimethylpiperazine ring.</p>	Last line treatment of dysmenorrhea	ADHD, smoking cessation	[33]
16	Propranolol	 <p>The chemical structure of Propranolol is shown. It consists of a naphthalene ring system. The 1-position of the naphthalene is substituted with a propyl chain that ends in an isopropylamino group (-NH-CH(CH₃)₂).</p>	Anti-hypertensive	Stage fright	[34]

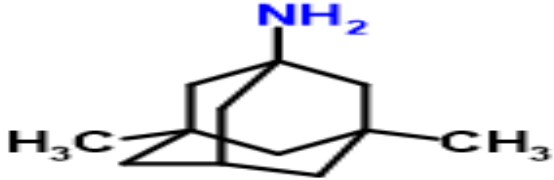
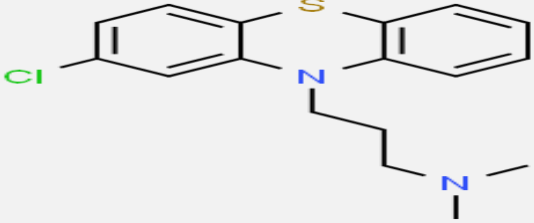
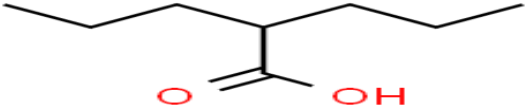
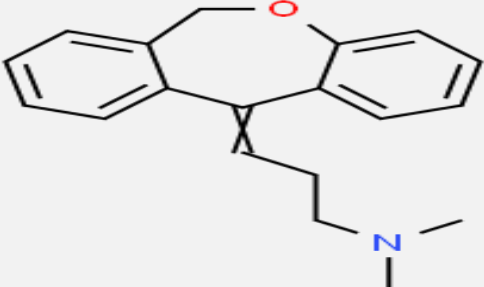
Table 4: CNS agents as an off-label drugs.

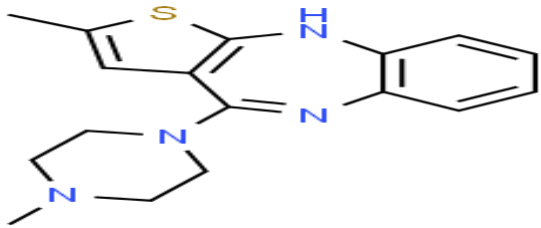
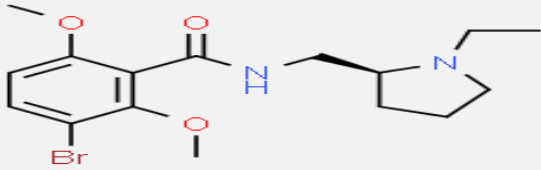
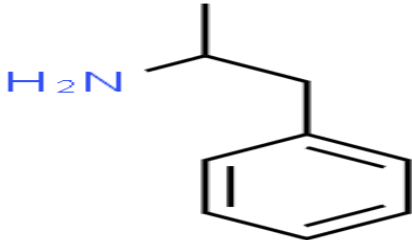
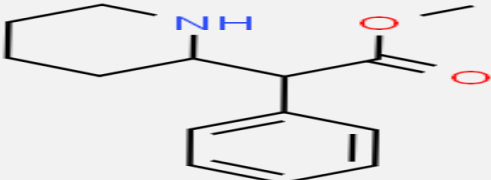
No.	Active constituent	Structure	On-label drug use	Off-label drug use	References
1.	Duloxetine		Anti-depressant	Urinary incontinence, chronic pain of myalgia and anti-anxiety	[35], [36]
2.	Lorazepam		Anti-anxiety	Anti-emetic	[37]
3.	Carbamazepine		Anti-convulsant	Schizophrenia, Second line treatment of bi-polar disorder	[38]

4.	Modafinil		Mind booster	Sexual retardation	[39]
5.	Amitriptyline		Anti-depressant	Chronic pain of fibromyalgia and sleep disturbance	[35]
6.	Milnacipran		Anti-depressant	Chronic pain of fibromyalgia	[35]
7.	Quetiapine		Schizophrenia	Bi-polar maintenance, sleep disturbance, insomnia, and sedation	[40]

8.	Escitalopram		Anti-depressant	Bi-polar	[41]
9.	Risperidone		Schizophrenia	Bi-polar maintenance	[42]
10.	Bupropion		Anti-depressant	Bi-polar	[43]
11.	Sertraline		Anti-depressant	Bi-polar	[43]

12.	Venlafaxine		Anti-depressant	Bi-polar	[43]
13.	Trazodone		Anti-depressant	Sleep-disturbance	[44]
14.	Clozapine		Anti-depressant	Depression	[45]
15.	Paroxetine		Anti-depressant in adult	Anti-depressant in children	[46]

16.	Memantine		Alzheimer	Obsessive compulsive disorder	[47]
17.	Chlorpromazine		Anti-psychotic	Anti-infective SARS, Covid, MERS	[48]
18.	Valproic acid		Epilepsy and bi-polar	Anti-cancer	[49]
19.	Doxepin		Anti-depressant Anti-anxiety	Hives (urticaria)	[50]

20.	Olanzapine	 The chemical structure of Olanzapine features a central benzothiazole ring system. It is substituted with a methyl group, a piperazine ring, and a phenyl ring.	Schizophrenia and anti-depressant	Sleep disturbance	[51]
21.	Remoxipride	 The chemical structure of Remoxipride consists of a benzene ring with a methoxy group, a bromine atom, and a methyl group. It is linked via a carbonyl group to a piperazine ring substituted with an ethyl group.	Anti-Psychotic	Anti-emetic	[52]
22.	Amphetamine	 The chemical structure of Amphetamine shows a benzene ring attached to a propan-2-amine chain.	Sympathomimetics	ADHD	[53]
23.	Methylphenidate	 The chemical structure of Methylphenidate features a piperidine ring connected to a phenyl ring, which is further substituted with a methyl ester group.	Sympathomimetics	ADHD	[53]

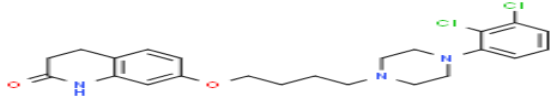
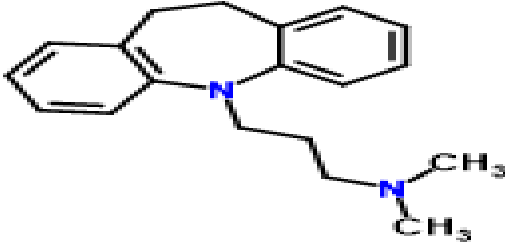
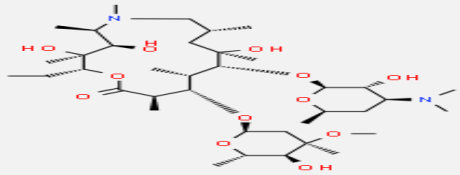
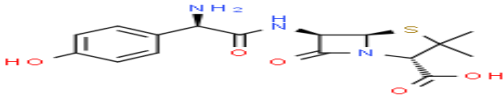
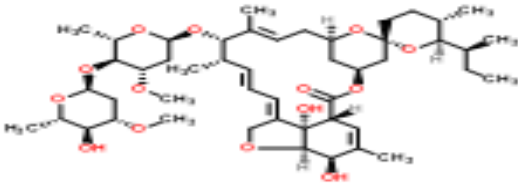
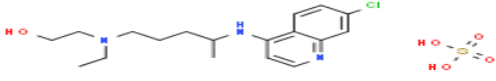
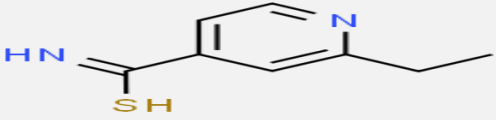
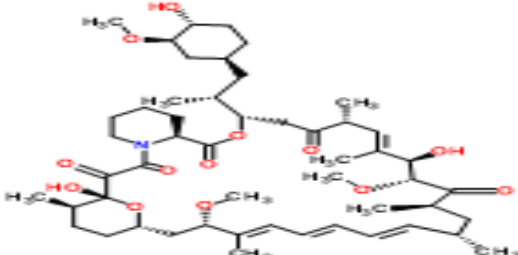
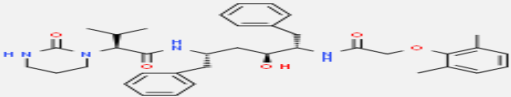
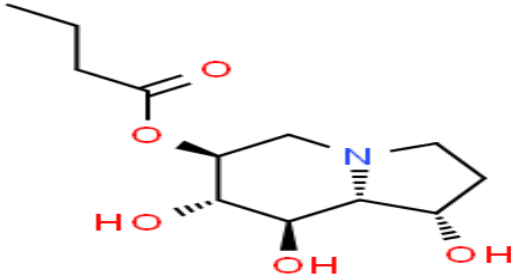
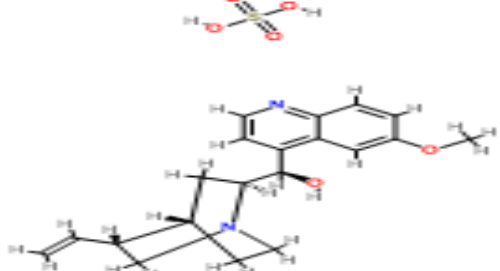
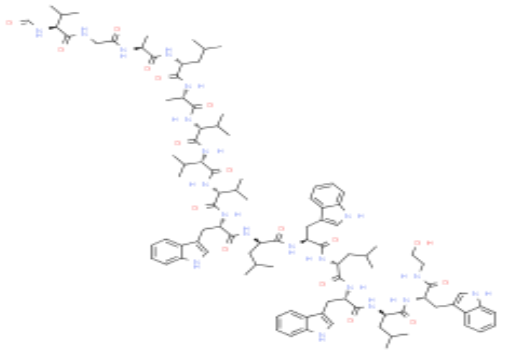
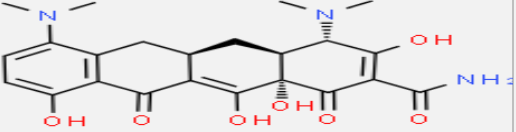
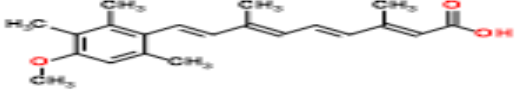
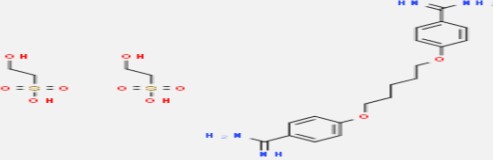
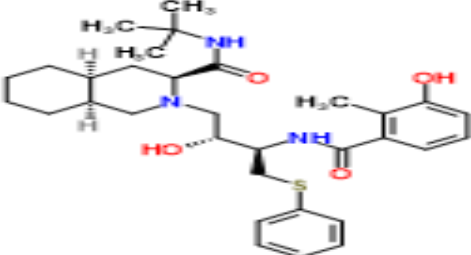
24.	Aripiprazole		Anti-psychotic	Dementia, Alzheimer's disease, schizophrenia	[54]
25.	Imipramine		Anti-depressant	Tempo mandibular joint disorder	[55]

Table 5: Anti-microbial as an off -label drugs.

No.	Active constituent	Structure	On-label drug use	Off-label drug use	References
1.	Azithromycin		Anti-biotic	Covid -19	[57]
2.	Amoxicillin		Anti-biotic	Otitis media on higher doses in children	[58]

3.	Ivermectin		Scabies	Covid-19	[59]
4.	Chloroquine		Anti-malarial	Covid-19	[60]
5.	Ethionamide		Multi-resistant tuberculosis	Anti-melanogenesis	[61]
6.	Rapamycin		Anti-fungal	Anti-cancer effect on T-cell inhibitor	[62]

7.	Lopinavir		Anti-viral	Anti-infective (SARS-and MERS-Covid inhibition)	[63]
8.	Celgosivir		Hepatitis C virus (HCV)	Dengue different viral infections	[64]
9.	Quinine sulphate		Anti-malarial	Inhibit different viral infections, heat shock protein 90 (HSP 90)	[65]
10.	Gramicidin A		Anti-bacterial	Anti-malarial	[66]

11.	Minocycline	 <p>The image shows the chemical structure of Minocycline, a tetracycline antibiotic. It features a central tetracycline core with two dimethylamino groups (N(CH₃)₂) at the 7 and 8 positions, and a dimethylaminoethyl side chain at the 4 position. The structure is color-coded with red for oxygen and blue for nitrogen.</p>	Anti-bacterial	Alzheimer's disease	[67]
12.	Acitretin	 <p>The image shows the chemical structure of Acitretin, a retinoid. It consists of a 1,3,5-trimethylphenyl ring attached to a long, branched polyene side chain that ends in a carboxylic acid group. The structure is color-coded with red for oxygen and blue for the methyl groups.</p>	psoriasis	Alzheimer's disease	[68]
13.	Pentamidine isethionate	 <p>The image shows the chemical structure of Pentamidine isethionate. It features a central pentamidine cation (a 4,4'-bis(2-dimethylaminoethoxy)azobenzene derivative) paired with two isethionate anions. The structure is color-coded with red for oxygen and blue for nitrogen.</p>	Trypanosomiasis and pneumocystis	Anti-malarial	[66]
14.	Nelfinavir	 <p>The image shows the chemical structure of Nelfinavir, a protease inhibitor. It features a piperidine ring system with a methyl group, a hydroxyl group, and a side chain containing a hydroxyl group, a methyl group, and a phenyl ring. The structure is color-coded with red for oxygen and blue for nitrogen.</p>	HIV protease (human immunodeficiency virus)	Anti-cancer	[11]

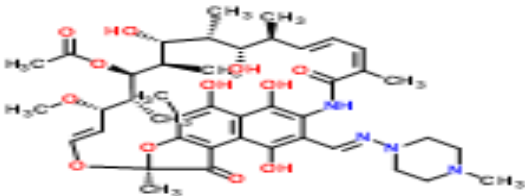
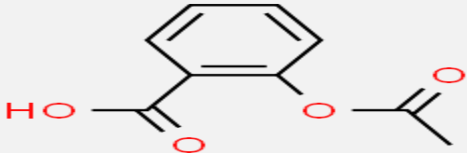
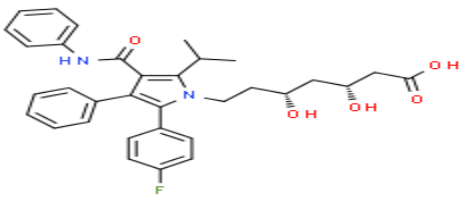
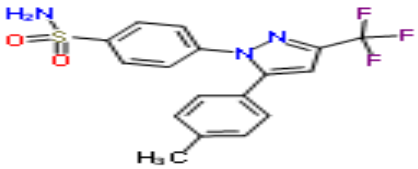
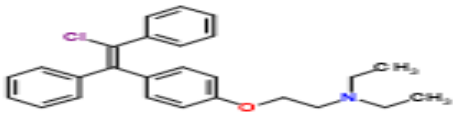
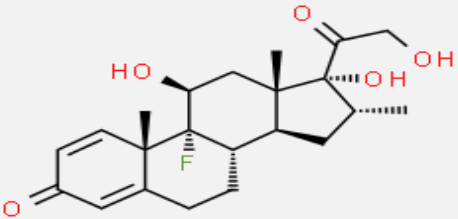
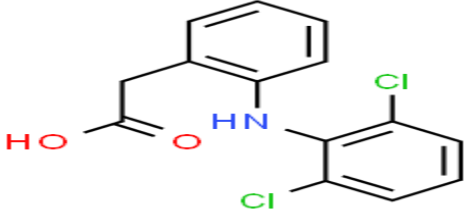
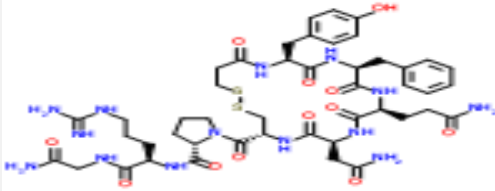
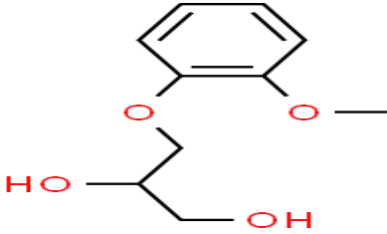
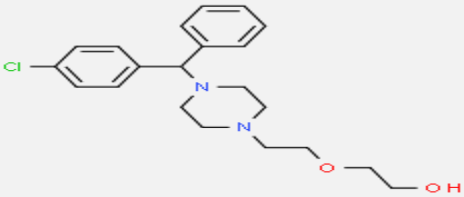
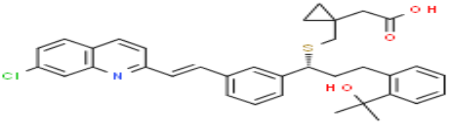
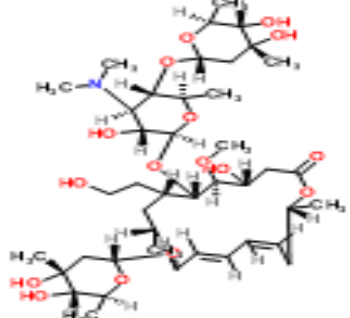
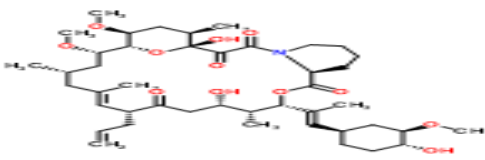
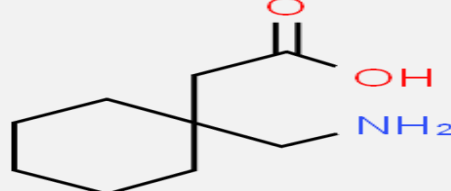
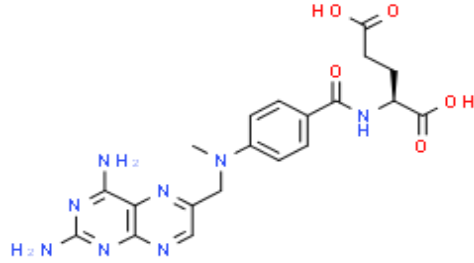
15.	Rifampicin		Anti-biotic	Enzyme induction in infant with biliary atresia	[69]
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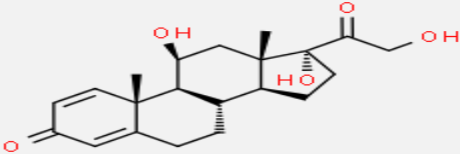
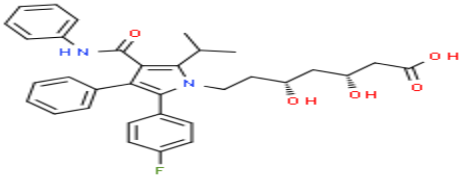
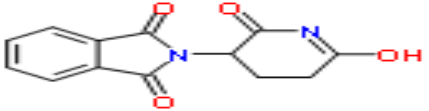
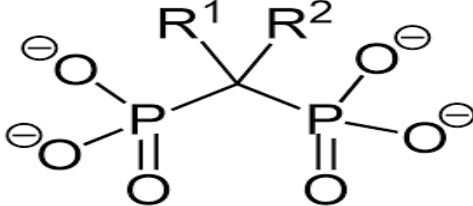
Table 6: Other miscellaneous off-label drug uses.

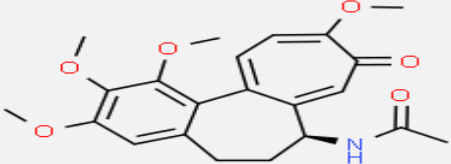
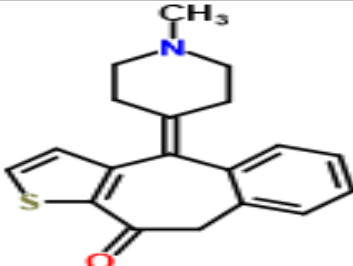

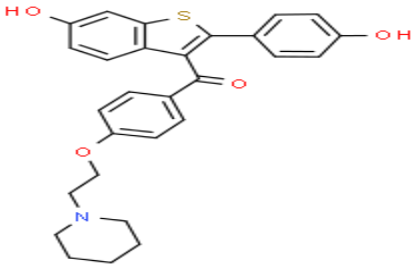
No.	Active constituent	Structure	On-label drug use	Off-label drug use	References
1.	Acetyl salicylic acid		Analgesic	Prevent colon cancer on the long run	[61]
2.	Atorvastatin		Control cholesterol level	Rheumatoid arthritis	[70]

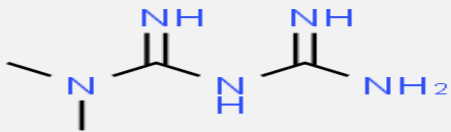
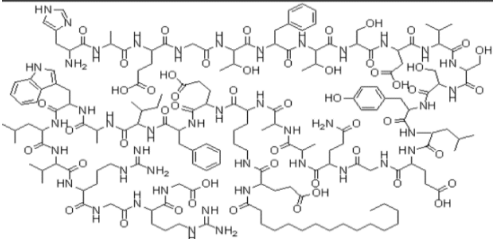
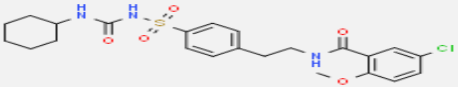
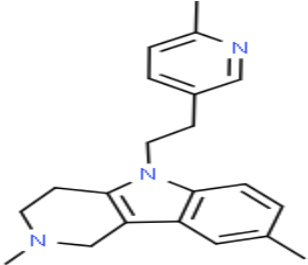
3.	Celecoxib		Joint pain	Fibromyalgia	[71]
4.	Clomiphene		Female infertility	Male infertility, anti-malarial	[66]
5.	Dexamethasone		Anti-inflammatory	Chemotherapy induced nausea and vomiting, enhance pulmonary maturation in labor	[72]
6.	Diclofenac		NSAIDs	Chronic pain associated with cancer patient along with amitriptyline	[73]

7.	Desmopressin		Anti-diuretic hormone	Nocturnal enuresis	[74]
8.	Guaifenesin		Anti-tussive	anti-convulsant, Sedation, ADHD	[75], [76]
9.	hydroxyzine		Allergy (all H1 blocker)	Sedation	[77]
10.	Montelukast		Asthma	COPD	[78]

11.	Epoetin alfa		Chronic renal failure	Anemia or chronic disease	[79]
12.	Tacrolimus		transplantation	Auto immune diseases	[80]
13.	Gabapentin		Partial seizures, nerve pain	Pain full diabetic neuropathy, herpes zoster	[81]
14.	Methotrexate		Non metastatic osteosarcoma, lung cancer, gestational carcinoma, epidermoid cancer of head and neck	For complete abortion, anti-cancer	[61]

15.	Prednisolone		Allergy, autoimmune disease	Dengue virus infection	[82]
16.	Statins		Hyperlipidemia	Colonic adenocarcinoma	[83]
17.	Thalidomide		Anti-emetic	Multiple myeloma and myelodysplastic syndrome	[84]
18.	Bisphosphonate		Reduce bone loss	Breast cancer	[10]

19.	Colchicine	 The chemical structure of Colchicine is a complex polycyclic molecule. It features a central decalin-like ring system with a nitrogen atom at the bridgehead. Attached to this system are a benzene ring with three methoxy groups, a pyridine ring, and a side chain containing a carbonyl group and a methyl group.	Gouty arthritis	Pericarditis	[85]
20.	Ketotifen	 The chemical structure of Ketotifen consists of a central seven-membered ring. This ring is substituted with a thiophene ring, a benzene ring, and a piperazine ring. The piperazine ring has a methyl group attached to its nitrogen atom.	Anti-allergic	Dengue viral infections	[86]
21.	Azelaic acid	 The chemical structure of Azelaic acid is a straight-chain dicarboxylic acid. It consists of a nine-carbon chain with carboxylic acid groups at both ends, represented as HO-C(=O)-(CH ₂) ₇ -C(=O)-OH.	Skin scrubber	Anti-viral	[87]
22.	Raloxifene	 The chemical structure of Raloxifene is a complex molecule. It features a central benzene ring with a sulfur atom at the 1-position. This ring is substituted with a hydroxyl group, a phenyl ring with a hydroxyl group, a carbonyl group, and a side chain containing a piperidine ring and a methoxy group.	Osteoporosis	Anti-malarial	[66]

23.	Metformin		Type 2 DM	Weight loss, Polycystic ovary syndrome	[88]
24.	Liraglutide	 <p>His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-N6-[N-(1-oxohexadecyl)-Glu]-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH</p>	Anti-diabetic	Weight loss	[89]
25.	Glibenclamide		Insulin secretagogue	Neonatal diabetes	[90]
26.	Dimebon		Anti-histaminic	Alzheimer's disease	[91]

Conclusion: -

Going to focus the light on the main broadline on terms of Off-label drug use. OLDU refers to prescribing a medication for a purpose other than its FDA-approved use. When the FDA approves a drug, it has undergone rigorous evaluation to ensure its safety and effectiveness for specific conditions. However, healthcare providers may sometimes use drugs off-label when no approved treatment exists for a particular disease or when existing treatments have been ineffective. Off-label use involves using a drug in ways not specified in its approved labeling. Examples include treating a different disease than the one it is approved for (e.g., using a chemotherapy drug for a different type of cancer) or administering it differently (e.g., using an oral solution instead of a capsule), use the drug for certain population rather than mentioned in the approval label (e.g., use of drugs for children rather than adult) and adjusting the dose (e.g., taking more tablets than recommended). When a drug is prescribed for an approved indication, there's strong scientific evidence supporting its use. The main reasons for using off-label drugs are lack of approval treatments. Sometimes, no FDA-approved drug exists for a specific condition or treatment resistance. Patients may not respond to approved therapies and medical judgment. Healthcare providers may consider off-label use if it is medically appropriate for a patient. The most common percentage from the top drug classes found on cardiac therapy, Anticonvulsants, antipsychotics, and antibiotics had the highest rates of off-label use in addition to use of OLDU in allergy, sedation, gynecological disorders, COPD, male infertility, female infertility, poly cystic ovary syndrome, fever, and weight loss. Unfortunately, many off-label uses lack strong scientific evidence. After the owner company began to approve the new therapeutic action, there would have to enter the drug into different clinical phases, and quality control tests to approve it. FDA approval ensures that a drug's benefits outweigh its risks for specific uses. Around 73% of off-label drug users were found to have little or no support. Off-label drug use has been a lifeline for many patients, especially during crises like Covid-19 pandemic and cancer treatment. To recap, usage of OLDU is case dependent and should have a risk, benefit comparison and comprehension to direct the decision towards people health.

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