WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Pyrimidine scaffolds in modern therapeutics: A comprehensive review

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ABSTRACT :

Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. Comprehensive research on diverse therapeutic potentials of heterocyclic compounds has confirmed their immense significance in the pathophysiology of diseases. The present review article aims to review the work reported on therapeutic potentials of pyrimidine scaffolds which are valuable for medical applications during new generation.

Keywords: Pyrimidine derivatives, anti-inflammatory, antimalarial, anticancer, antidepressant.

INTRODUCTION:

Heterocyclic compounds

In chemistry, particularly organic chemistry, heterocycles are thought to make up the majority of the subject. Heterocyclic rings are an essential component of the molecules that make up the majority of natural chemicals created by biotic components. The health of humans and animals is affected by a variety of commercially significant substances, including cardiac glycosides, various insecticides, antibiotics like cephalosporin and penicillin, and alkaloids like vinblastine, reserpine, morphine, and ellipticine. Synthesizing novel heterocycles that mimic natural compounds with similar biological activity has led to the majority of significant improvements being made. Because of this, communities of scientists, researchers, and chemists are constantly working to create better weed killers, insecticides, compost, fungicides, and pesticides. Heterocycles have important uses in vulcanization accelerators, antioxidants, dyestuffs, photographic material, data storage, plastics, additives, data storage, and photography, in addition to the current way of life and civilization. Ultimately, there are countless remarkable molecules to be found in heterocyclic chemistry. Many models with different biological, physical, and chemical features can be created for carbon, heteroatoms, and hydrogen. Organic chemistry is a large field that is being strengthened by the discovery of novel techniques and the planned application of established methods for the synthesis of heterocycles[1].

PYRIMIDINE:

Similar to pyridine, pyrimidine is an aromatic heterocyclic chemical molecule. Having two nitrogen atoms in the ring[2], this compound is one of the three diazines, which are six-membered heterocyclics with the nitrogens located at positions 1 and 3.2 Pyrazine[3] (nitrogens 1 and 4) and pyridazine (nitrogens 1 and 2) are the other two diazones. Uric acid breakdown products were identified as pyrimidine (also known as "m diazine"). Alloxan was the first pyrimidine derivative to be isolated by Brungatelli in 1818[4]. Pinner was the first to use the term "pyrimidine," which combines the terms "pyridine" and "amidine".

THE CHEMISTRY OF PYRIMIDINE RING:

The structure of pyrimidine

Pyrimidine is a crucial aromatic heterocyclic ring with six members and two nitrogen atoms. It is considered one of the fundamental building blocks of nucleic acids, such as DNA and RNA, and is involved in several key biochemical processes in living organisms. Pyrimidine is a heterocyclic compound that is formed by replacing two C-H units meta to each other in a benzene ring with nitrogen atoms. This process results in a decrease in the symmetry of the benzene ring and uneven bond lengths. However, despite this decrease in symmetry, pyrimidine still retains symmetry around the 2 and 5 axes, resulting in three distinct pairs of identical bond density centers for the p-electrons. This is in contrast to benzene, where the electrons are evenly dispersed across the ring system. Due to the differing reactivities of the carbon atoms at positions 2, 4, 5, and 6 of pyrimidines and the substituents attached to them, the substituent effects on the reactivity of these carbon atoms differ.

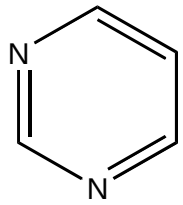


Fig 1. Pyrimidine

3.2. The electronic structure and geometry of pyrimidine ring

The pyrimidine ring is not three-dimensional, but rather flat. In pyrimidine, compared with the other two diazones: pyrazine and pyridazine, the ortho and para positions of the nitrogen atom, which is electronegative, exhibit a more notable decrease in electron density. This is because the two "N" atoms of this 1,3-diazine are positioned in such a way that their respective effects reinforce each other, thus acting synergistically. Pyrimidines have a greater impact than their isometric counterparts due to non-additive electronic effects of the two "N" atoms, which can sometimes even be antagonistic to each other. The pyrimidine ring (2) has three positions marked with (*), namely C-2, C-4, and C-6. These positions become highly electropositive centers as a result. However, the C-5 position still retains some electronegativity, but to a lesser degree. Additionally, the localization of p electrons on the two "N" atoms leads to a reduction in the aromaticity of the pyrimidine ring. Pyrimidines lack complete aromaticity due to the presence of a non-participating nitrogen atom. As a result, only partial aromaticity is observed at the C-5 position, leading to a considerable reduction in the molecule's stability. This is reflected in a low resonance energy of only 26 kcal/mol[5].

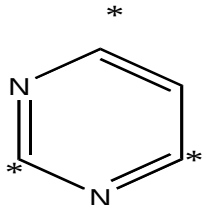


Fig 2

3.3. The pKa of pyrimidine

Pyrimidine, a diazine compound, exhibits weaker basicity (pKa 1.31) as compared to pyridine (pKa 5.2). This is due to the sharing of p-electrons between the first and second ring nitrogens, resulting in an approximate structure of 3-nitropyridine (pKa 0.8). Pyrimidine's basicity lies between that of pyridazine (pKa 2.33) and pyrazine (pKa 0.6), two isometric diazine compounds. This is because the ring nitrogen in pyrimidine no longer has the ability to attract p-electrons, which affects its basic strength[5].

3.4. The electrophilic attack

Pyrimidine is typically attacked by electrophilic reagents at its C–5 positions, which are the least electron-depleted sites. This compound can be readily subjected to a variety of reactions, such as nitration, nitrosation, halogenation, sulfonation, and coupling with diazonium salts[5].

3.5. The nucleophilic attack

Direct nucleophilic substitution of hydrogen at the C-2, C-4, and C-6 positions of the pyrimidine ring is considered the most effective approach for targeting these positions. However, despite its potential, this reaction is relatively rare, and only a limited number of examples of direct nucleophilic attack on pyrimidine rings are known[5].

STRUCTURE ACTIVITY RELATIONSHIP OF PYRIMIDINES :

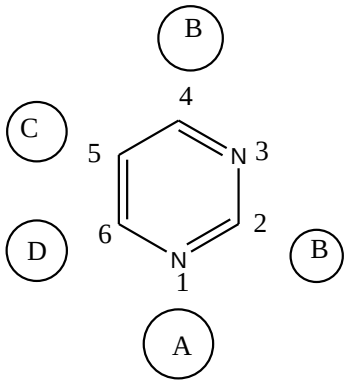


Fig 3

- The molecular properties responsible for receptor affinity and selectivity can be better understood through SAR (Structure-Activity Relationship) studies. Compounds with promising potential can be attributed to substitutions made at the hydrophobic domain[6].
- The hydrophobic aryl ring in the compounds under investigation was substituted with electron-withdrawing and donating groups at the ortho, meta, and para positions. It was observed that the substituted derivatives exhibited higher activity compared to the non-substituted ones[7].
- The reason for this phenomenon could be attributed to the superior fitting of substituted derivatives into the receptor site.

Position A

The substitution of a five-membered saturated heterocyclic ring has been found to exhibit promising anticancer and antiviral activities[6.]

Position B

i. When a substitution occurs at the 2nd position of a molecule with a five or six-membered saturated heterocyclic ring, it directs the molecule towards exhibiting anthelmintic, antiparkinsonian, and expectorant activity, as well as aiding in the treatment of gastrointestinal (GI) disturbances.

ii. The substitution of keto or amino groups in the 2nd and 4th positions or a combination of both in a molecule leads to the development of potent compounds with diverse biological activities such as anticancer, antiviral, antibacterial, and antifungal properties. These compounds are also effective in the treatment of respiratory tract infections and liver disorder[s8.]

Position C

Introduction of a substituted amine, saturated distal heterocyclic ring, or halogen at the 5th position has been observed to result in significant antibacterial and anticancer activities.

Position D

The fifth and [sixth] position of a heterocyclic ring are fused with another heterocyclic ring, and the ortho, meta, and para positions are substituted with an aryl ring. This type of substitution has been found to exhibit potent anticancer, antiviral, and antibacterial properties. Additionally, it has shown promise in vasodilation and in the treatment of urinary tract infections[6].

BIOLOGICAL SIGNIFICANCE OF PYRAMIDINE SCAFFOLDS:

Anti-Convulsant and Anti-Depressants Properties of Pyrimidine Derivatives

Anticonvulsants and antidepressant are commonly used drugs for treating CNS disorders. A study was conducted to examine the antidepressant and anticonvulsant properties of series of 5-alkoxytetrazolo[1,5-c] thieno [2,3-e] pyrimidine derivatives. The most effective compound at a dosage of 100 mg/kg was found to be 5-(2,4-dichlorobenzyloxy) tetrazolo[1,5-c] thieno [2,3-e] pyrimidine, which reduced the immobility time by 51.62 percent. Wang et al. produced a series of 5-alkoxytetrazolo [1,5-c] thieno [2,3-e] pyrimidine derivatives (Fig. 4). The maximum electroshock (MES) and forced swimming tests (FST) were evaluated using their antidepressant and anticonvulsant properties[9].

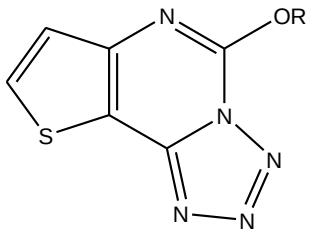
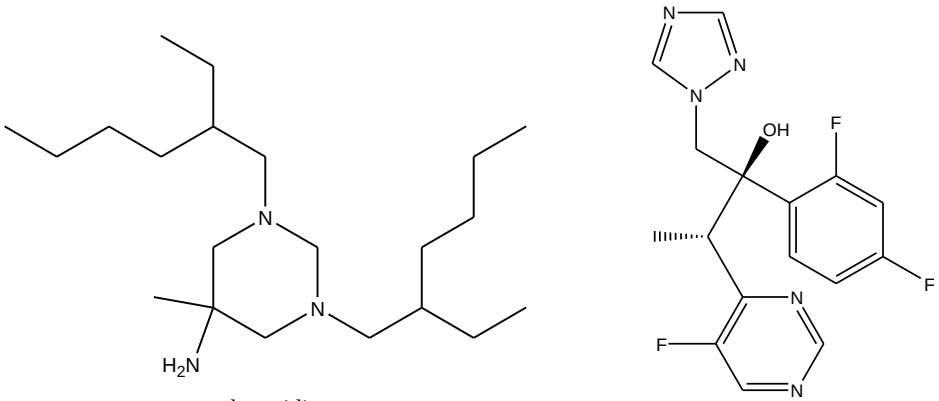


Fig. 4 Structure of 5-alkoxytetrazolo [1,5-c] thieno [2,3-e] pyrimidine

Antifungal Drugs:

Pyrimidines also have beneficial antifungal properties (Figure 5). Flucytosine, a fluorinated pyrimidine, is an orally active antifungal drug used to treat significant systemic infections caused by specific strains of Candida and Cryptococcus, whereas hexetidine is used primarily to treat aphthous ulceration. Voriconazole, a disubstituted medication, is currently undergoing phase I comparative clinical trials to demonstrate its full potential as a broad-spectrum antifungal treatment[10].



hexetidine voriconazole

Fig .5

Antimicrobial

Antimicrobial activity microbes cause a variety of disease including amoebiasis pneumonia malaria typhoid common curve and cold certain serious disease such as tuberculosis influenza syphilis and AIDS[11]. Over time, numerous techniques have been employed to investigate the pyrimidine moiety's efficacy as an antibacterial agent. In 1948, Hitchings made an impactful breakthrough when he found that large number of2,4-diaminopyrimidines, along with various 2-amino-4-hydroxypyrimidines, function as folic acid antagonists. It was subsequently discovered that these pyrimidines could inhibit the enzyme dihydrofolate reductase (DHFR). Among the two 4-diaminpyrimidine medicines, pyrimethamine selectively inhibits the DHFR of malarial plasmodia. Trimethoprim (figure 6) is an antibacterial medication that preferentially inhibits bacterial DHFR[12]**.**

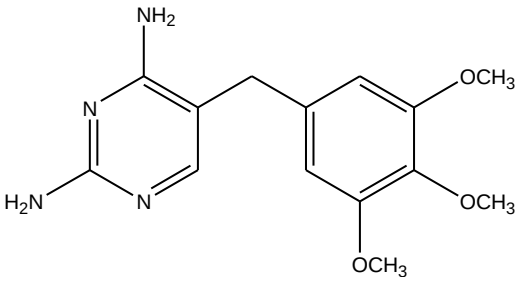
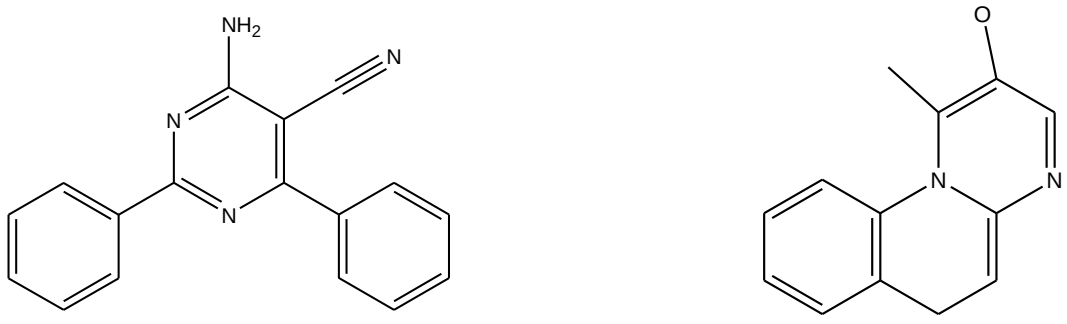


Fig.6 Trimethoprim

Anti-inflammatory activity

Nonsteroidal anti-inflammatory drugs (NSAIDs) are significant in managing various painful conditions such as rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections, and fever. Unlike opioid analgesics, NSAIDs do not interact with opioid receptors but rather provide pain relief by exhibiting anti-inflammatory properties and antipyretic action. 4 amino-5-cyano-2, 6-diphenylpyrimidine (1) derivatives were reported to be twice as active as acetylsalicylic acid (Falcao et al., 2006). Also, 6-indolylideneamino-2-thiouracile has stronger anti-inflammatory action than Ibuprofen (Mohamed et al, 2010a). Naphtho [2, 1-b] furo [3, 2-d] pyrimidine (2) (fig. 7) was claimed to be anti-inflammatory. (Padmashali et al. 2002). Thieno tetrazolopyrimidines and thieno-triazolo-pyrimidine were found to have strong anti-inflammatory properties in Carrageenan-induced inflammation (Rashad et al., 2005)[9].The anti-inflammatory properties of the pyrimidin-2-amines were evaluated in Balb/c mice that had been subjected to localized edema. Four compounds have been shown to have more effective anti-inflammatory activity than the others: four-(9H-Fluoren-2-yl)-6-phenylpyrimidin-2 amine, four-(4-[diphenylamino] phenyl) pyrimidine-2-amine, three-(3-[9H-Fluoren-2-yl]1-yl-3-oxoprop-1en-1One (Kumaresan et al., 2014) is the -4H-chromen[4].



(1) (2)

Fig. 7

Antidiabetic activity

A series of newly synthesized pyrimidine derivatives containing thiazolidine dione were tested for their ability to reduce glucose and lipid levels. The reference compounds used for comparison were pioglitazone and rosiglitazone[13].Synthesized azolopyrimidine derivatives and compounds were evaluated for hypo-glycemic activity[14].

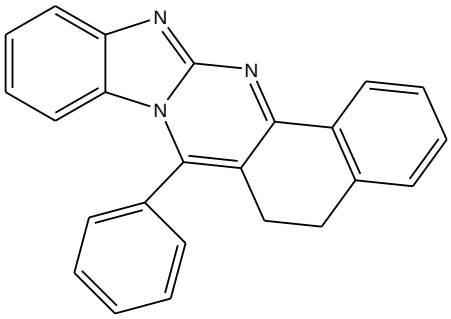
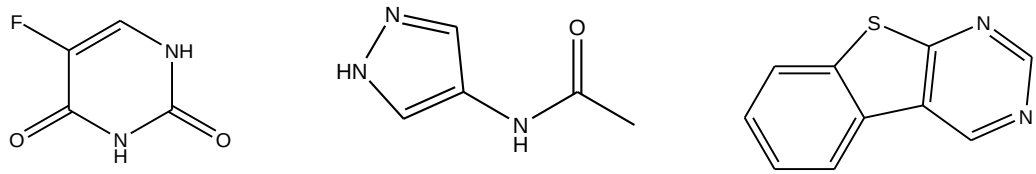


Fig.8 Azolopyrimidine

Anticancer activity

Pyrimidine substitutes have demonstrated promising results in the fight against cancer. The structural modification can pertain to either the pyrimidine ring or the attached sugar groups. Early metabolite prepared was 5 fluorouracil (1) (Callery et al., 2002), a pyrimidine derivative which also exhibits some useful antineoplastic activities (Al Safarjalani et al., 2005) The inhibitors of mammalian target of Rapamycin (mTOR) kinase are based on quaternary substituted dihydro furo pyrimidine derivatives. The compound with 4-acetamido pyrazole moiety (2) was found to be most potent (Cohen et al., 2011). The scaffold (3) with tricyclic benzo [4, 5] thieno [2, 3-d] pyrimidine structure (fig.9) functions as a dual inhibitor of both thymidylate synthase and dihydrofolate reductase (DHFR)inhibitor[15].



(1) (2) (3)

Fig.9

Antibiotic activity

Antibacterial antibiotics are classified based on their target specificity as either "narrow-spectrum" or "broad-spectrum." Narrow-spectrum antibiotics are designed to target specific types of bacteria, such as Gram-negative or Gram-positive bacteria. On the other hand, broad-spectrum antibiotics are

formulated to affect a wide range of bacteria. Antibiotics target the bacterial cell wall (penicillins, cephalosporins) (Fleming et al., 1929), or cell membrane (polymixins) (Dixon et al., 1986) or interfere with essential bacterial enzymes (quinolones, sulfonamides). These are usually bactericidal in nature. Those which target protein synthesis such as the amino glycosides, macrolides and tetracyclines are usually bacteriostatic in nature (Champney et al., 2001). There are few examples of antibiotics containing pyrimidines moiety. Bacimethrin (5 hydroxymethyl-2-methoxypyrimidin-4-amine) (fig.10), is active against several staphylococcal infections (Reddick et al., 2001). Gourgetin[16], a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria (Singh et al., 2003). Derivatives of cytosine, namely amicetin and plicacetin exhibit activity against acid fast and Gram-positive bacteria (Reddick et al., 2001)[17]. Aminoglycoside antibiotics phleomycin, bleomycin and related families are wide-spectrum antibiotics containing the pyrimidine ring[18].

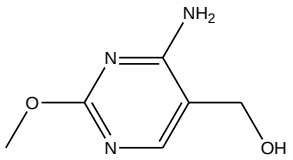


Fig .10

Antithyroid properties of pyrimidine derivatives

A study by Lacotte et al. delved into the process of biosynthesis of iodinated hormones T3 and T4. Their findings revealed that the translocation of iodide into thyroid cells is the crucial first step in this process. In this study, the researchers investigated the inhibition of iodide entrapment in rat thyroid cells using dihydropyrimidin-2-ones (DHPMs) synthesized through the multicomponent Biginelli reaction. The sodium iodide symporter (NIS), a glycoprotein present in various tissues such as the thyroid gland, salivary glands, gastric mucosa, and mammary glands during lactation, was the primary focus of their investigation. The DHPMs were found to be effective in inhibiting iodide entrapment in rat thyroid cells. Through a cell-based experiment, the team evaluated the potential of twelve compounds to inhibit the sodium iodide symporter (NIS). One derivative displayed unusually robust behavior, with a half maximum inhibitory concentration value (IC50) of 65 pM. This research contributes to the advancement of developing anti-thyroid agents[9].

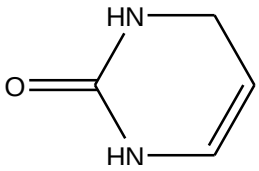


Fig .11 Structure of dihydropyrimidin-2-ones

The clinical and pharmacological uses of Pyrimidine in the microbial world

Many pyrimidine derivatives that have been produced during the past 20 years are found to have numerous therapeutic and pharmacological uses19
Antibacterial agents: This class of medications includes sulfa drugs, which are pyrimidine derivatives containing sulfur , and antifolates, which have antagonistic action against folic acid20.
Antagonists of folic acid are found to be 2-amino-4-hydroxypyrimidines. Thus, a considerable amount of 2,4-diaminopyrimidines have been synthesized as antifolates. Eventually, it was demonstrated that these pyrimidines function as inhibitors of dihydrofolate reductase (DHFR)21. The following drugs are noteworthy within the group of 2,4-diaminopyrimidines.
Brodiprim (1), a trisubstituted pyrimidine-containing drug, has been identified as an effective antibacterial compound. Recently, a new selective dihydrofolate inhibitor called Iclaprim (2) was synthesized using rational drug design principles. This drug has demonstrated activity against bacterial strains that are resistant to methicillin, trimethoprim-sulfamethoxazole (TMP), and vancomycin22. Trimethoprim (3) is a potent antibacterial agent that functions by selectively blocking the activity of bacterial dihydrofolate reductase (DHFR), an enzyme that is crucial for the survival and replication of bacterial cells.
Pyrimethamine (4) is a tetrasubstituted pyrimidine-containing drug that acts as a highly effective inhibitor of the dihydrofolate reductase (DHFR) enzyme found in malarial plasmodia. It has been proven to be a potent antimalarial drug due to its ability to inhibit the synthesis of tetrahydrofolate, a necessary component for the synthesis of DNA and RNA in malarial parasites (fig.12).
Antibiotics that contain a pyrimidine moiety are categorized based on the substitution on the ring.
Amicetin (5) is a type of antibiotic drug that contains disubstituted pyrimidine. This drug is a derivative of cytosine and has been found to efficacy against acid-fast bacteria, Gram-positive bacteria, and other microorganisms (fig.13) [21].
Phenacetin (6) is a substance that originates from cytosine, and it has the ability to combat bacterial infections. In contrast, bacimethrin (7) is an antibiotic that belongs to the pyrimidine class and is effective in treating various types of staphylococcal infections[23].

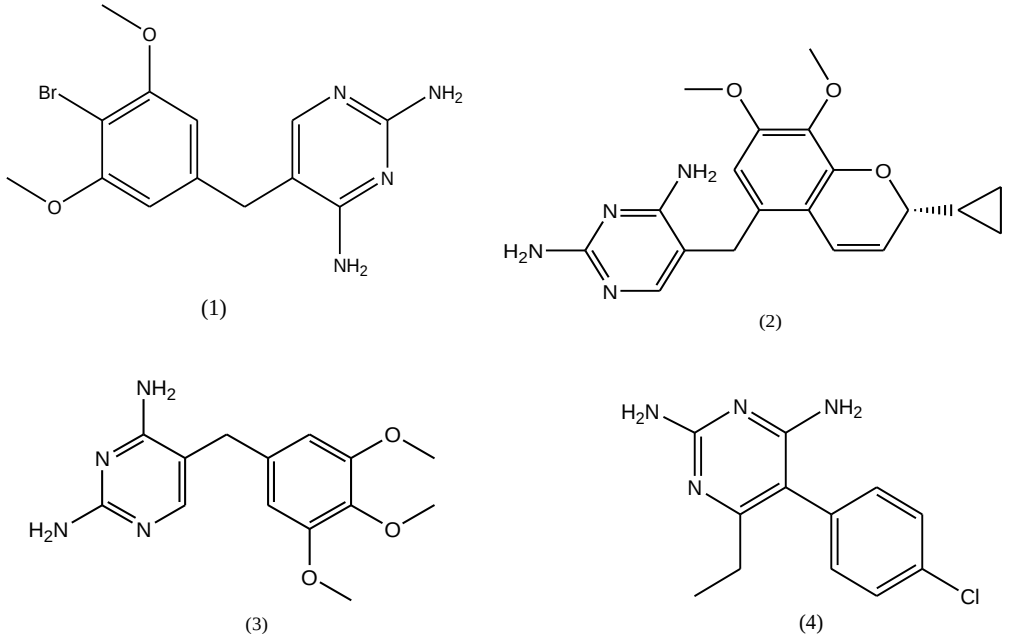


Fig .12 Antibacterial drugs (antifolates) containing trisubstituted and tetrasubstituted pyrimidines

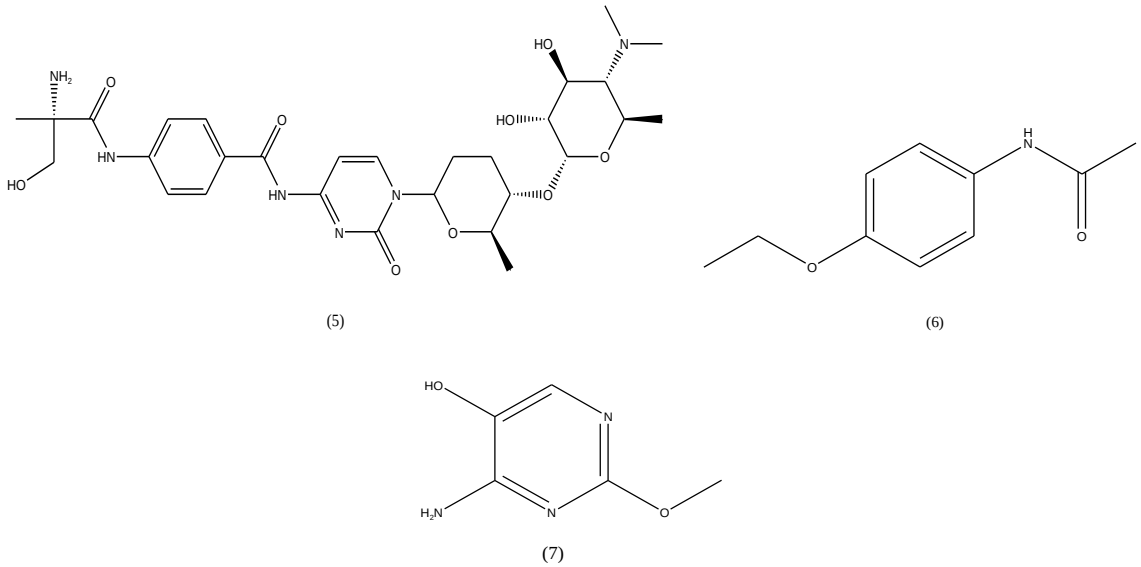


Fig.13 Antibiotics representing disubstituted (5) pyrimidine moiety and trisubstituted (6-7) pyrimidine moiety.

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