BIOLOGICAL ACTIVITIES OF SYNTHETIC PYRIMIDINE DERIVATIVES

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ABSTRACT

Heterocyclic chemistry is a rapidly expanding branch of organic chemistry. Nitrogen, sulphur and oxygen are the most common heteroatoms present in the heterocyclic ring. Nitrogen containing heterocycles are widely distributed in nature and are the constituents of diverse group of essential molecules from antibiotics to vitamins and are a vital part of nucleic acids. Literature survey indicated that pyrimidine derivatives have a wide range of pharmacological activities making them popular candidates for drug discovery protocols. Synthetic derivatives of pyrimidines have been shown to have antihyperuricemic, anti cancer, anti-inflammatory, antibacterial, antifungal, antiviral, antioxidant, anticonvulsant, anti tubercular, antibiotic, analgesic, antipyretic, antihypertensive, antihistaminic, antiallergic, antileishmanial, antidiabetic, herbicidal, central nervous system depressant, and calcium channel blocking activities to name a few. Pyrimidine derivatives will continue to be a source of new drugs to treat the ever increasing burden of diseases. Some of the important biological activities are described in this review.

KEYWORDS: Heterocycles, Pyrimidine derivatives, Biological properties, Anticancer, Cardiovascular, CNS, Antimicrobial, Immunological.

INTRODUCTION

The chemistry of heterocycles is most complex and diverse branch of organic chemistry, and is a rapidly growing area of chemistry because of wide applications of these compounds in

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pharmaceuticals, agriculture and industry (Kidwai et al., 2003; Jain et al., 2006). They find applications in cosmetics, reprography, information storage, plastics, electronics, optics and material sciences (Valverde et al., 2005). Nitrogen, sulfur and oxygen are the most common heteroatoms present in heterocyclic rings. Nitrogen containing heterocycles are the most abundant due to their wide distribution in nucleic acids. The nitrogen containing heterocyclic compounds in nucleic acids are of two main groups, the purines and pyrimidines. Pyrimidines are six-membered heterocyclic aromatic organic compounds containing two nitrogen atoms in the benzene ring (Barreca et al., 2001). They are widely found in nature in various forms and are the building blocks of numerous natural compounds from antibiotics to vitamins besides being vital components of nucleic acids. Nucleic acid hydrolysis yields several pyrimidines such as cytosine, thymine and uracil. While cytosine is present in both DNA and RNA, uracil present only in RNA and thymine only in DNA (Agarwal, 2006). Hundreds of pyrimidine containing compounds has been found in biochemistry. The different modifications possible in this scaffold continue to be an interesting subject to the medicinal chemist by virtue of their diverse biological activities.

Pyrimidine derivatives have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy. Several hydro and oxo derivatives of these are particularly important in biological systems. Pyrimidine nucleus is found in Alloxan (1) is known for its diabetogenic action in a number of animals (Eussell, 1945).

![Image of Alloxan](image1)

(1)

The pyrimidine nucleus also constitutes the major part of vitamins such as thiamine (2) (Bettendorff et al., 2007), riboflavin (3) (Zempleni et al., 1996), and folic acid (4) (Bailey et al., 2009).
Literature survey indicated that pyrimidine derivatives have a wide range of pharmacological activities making them popular candidates for drug discovery protocols. Various analogs of pyrimidines have been found to possess diverse biological activities such as anti hyperuricemic (Pacher et al., 2006; Evenas et al., 2014), anti cancer (Al Safarjalani et al., 2005; Devegowda et al., 2010), anti-inflammatory (Goudar et al., 2012; Kumaresan et al., 2014), anti bacterial, antifungal (Hussain et al., 2013; Kumar et al., 2006), antiviral (Hilmy et al., 2011; Turner et al., 1999), antioxidant (Dudhe et al., 2015a; Bano et al., 2012), anticonvulsant (Gupta et al., 1994; Valarmathy et al., 2011), anti tubercular (Chandrashekaraiah et al., 2014; Siddiqui et al., 2014), antibiotic (Fleming et al., 1929; O Stanisaw., 2009), analgesic (Goudgaon et al., 2014), antipyretic (El-Hawash et al., 2006; Keri et al., 2010), antihypertensive (Ganzevoort et al., 2004; Wong et al., 1994), antihistaminic, anti allergic (Del Cuvillo et al., 2007; Ikeda et al., 1996), anti leishmanial (Ram et al., 1992) anti diabetic (Lee et al., 2005) and herbicidal (Fan et al., 1996). They have also been found to possess central nervous system (CNS) depressant properties (Brunton et al., 2005) and also act as calcium channel blockers (Kumar et al., 2002). Some of the important biological activities are described in this review.

Anticancer activity
Substituted pyrimidines show promising anticancer activity. The structural modification may be on the pyrimidine ring or on the attached sugar groups. Early metabolite prepared was 5-fluorouracil (5a) (Callery et al., 2002), a pyrimidine derivative followed by 5-Thiouracil (5b) 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 dihydrofuropyrimidine derivatives. The compound with 4-acetamido pyrazole moiety (6) was found to be most potent (Cohen et al., 2011). Tricyclic benzo [4, 5] thieno [2, 3-d] pyrimidine scaffold (7) acts as dual thymidylate synthase inhibitor and dihydrofolate reductase (DHFR) inhibitor.
The pyrazolo [1, 5-α] pyrimidines, triazolo [1, 5-α] pyrimidines and pyrimido [1, 2-α] benzimidazole ring systems incorporating phenyl sulfonyl moiety shows Aurora-A kinase inhibitor activity thereby effectively arresting the cell cycle progression. 2,7-Diphenyl-6-(phenylsulfonyl)pyrazolo[1,5-α]pyrimidine (8) and its p-methoxy analogue were found to be cytotoxic against HST116 colon tumor cell line and was equipotent to Doxorubicin as a reference drug (Shaaban et al., 2011). Some pyrazolo [3, 4-d] pyrimidines (9) electrophilic and nucleophilic compounds have been evaluated for their potential cytotoxicity against breast cancer cell line (MCF7), which show high activity (Ibrahim et al., 2011).

Capecitabine (10) (Xeloda®) is an orally administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers. Capecitabine is a prodrug and enzymatically converted to 5-FU in the tumor, where it inhibits and slows the growth of tumor tissue (Galmarini et al., 2002). A series of 4-anilino-2-(2-pyridyl) pyrimidines have also been found to be potent inducers of apoptosis (Sirisoma et al., 2006). The pharmacokinetic and preclinical properties of the 5-chloro-6-methylene-thiocarboxamidine derivatives showed that potent antitumor activity in colorectal and breast cancer (Yano et al., 2004). 5-Fluoro-1-(2-tetrahydrofuryl)-uracil (11) (Tegafur®, Ftorafur®), a prodrug of 5- FU, has been widely used for the treatment of cancer because of its low toxicity relative to 5-FU (Blokhina et al., 1972). Tegafur is used orally as postoperative chemotherapy for breast, gastric and colorectal cancers, and treatment of various types of metastatic solid tumors (Pedikian et al., 1983).
The pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-5-ones bearing different substituent at position 3 were examined for cytotoxic activity. Some of these compounds exhibit good antitumor activity against MCF7 compared with doxorubicin (El-Nassan., 2011).

**Anti-inflammatory activity**

Anti-inflammatory drugs have a very important clinical use in the treatment of various painful conditions such as rheumatoid arthritis, soft tissue lesions, oral cavity lesions, respiratory tract infections and fever. In contrast to opioid analgesics, NSAIDs relieve pain without interacting with opioid receptors, reduces the body temperature (antipyretic effect), and possess anti-inflammatory property. 4-Amino-5-cyano-2, 6-diphenylpyrimidine (12) derivatives were reported to be twice as active as acetylsalicylic acid (Falcao et al, 2006). Also the 6-indolylideneamino-2-thioracile displayed more potent anti-inflammatory activity than Ibuprofen (Mohamed et al, 2010a). Naphtho [2, 1-b] furo [3, 2-d] pyrimidine (13) was reported as anti-inflammatory agents. (Padmashali et al, 2002). Thieno tetrazolopyrimidines and thienotriazolopyrimidine were tested to shows significant anti-inflammatory activities in Carrageenan induced inflammation (Rashad et al., 2005).

![Chemical structure of (12)](image1.png)

![Chemical structure of (13)](image2.png)

The pyrimidin-2-amines were tested for the anti-inflammatory activity against Balb/c mice with locally induced edema. The compounds, 4-(9H-Fluoren-2-yl)-6-phenylpyrimidin-2-amine, and 4-(4-[diphenylamino] phenyl) pyrimidine-2-amine are found to have more efficient anti-inflammatory activity than that for 4, 6-Bis-(9H-fluoren-2-yl)pyrimidin-2-amine, and 3-(3-[9H-Fluoren-2-yl]-3-oxoprop-1-en-1-yl)-4H-chromen-4-one (Kumaresan et al., 2014).

**Antibacterial and Antifungal activity.**

The re-emergence of multi-drug resistant microbial and fungal infections in the past few years has become a serious concern. This has lead to a search for new antimicrobial and antifungal agents with improved biological activity. Pyrimidine salt, namely, 4-methyl-3-(4-
pyridin-3-ylpyrimidin-2-ylamino)-phenyl ammonium-2, 5-dichloro-4-hydroxy-3, 6-dioxo-cyclohexa-1, 4-dienolate (14) chloranilic acid was found to have good anti bacterial and anti fungal activity in vitro. (Mallikarjunaswamy et al., 2013). Flucytosine (15) is a fluorinated pyrimidine and is used as nucleosidal antifungal agent for the treatment of serious systemic infections caused by susceptible strains of Candida and Cryptococcus (Smith et al., 2008; Chadwick et al, 1991).

Mercaptopyrimidine and aminopyrimidine derivatives of indoline-2-one were screened for their in vitro antibacterial activity against Gram-positive bacteria Staphylococcus aureus, Bacillus subtilis and Gram-negative bacteria Salmonella typhi, Shigella dysenteriae, Pseudomonas mirabilis, and Escherichia coli. It was found that compounds (16) and (17) with a methoxy (OCH$_3$) substituttion on phenyl ring at para position, hydroxyl (-OH) group at ortho position and -Cl substitution showed very good inhibition at concentration of 100 µg/mL against both Gram-positive and Gram-negative bacteria compared with the standard drug Ampicillin (Mondal et al., 2010). Similarly 3,4-dihydro-1-(tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-one (Dudhe et al., 2015a) and 2-(4-substituted benzylthio)-5-amino-6-(benzo[d]thiazol-2-yl)-7-(4-chlorophenyl)pyrido [2,3-d] pyrimidine-4(3H) one showed antifungal activity in various strains of fungi.
The aminopyrimidines bearing benzofuran rings were screened for their in vitro antibacterial activity against *P. aeruginosa* and *S. Aureus* and antifungal activity against *A. niger* and *Curvularia*. Compound (18) showed antimicrobial activities comparable with chloramphenicol and fluconazole (Kumar et al., 2006). Azoxytrobin (19) and its derivatives (Clough et al., 1996) and fluoxastrobine (Jordi et al., 2006) are potent fungicides commonly used in agriculture. These are environmentally safe and used for protecting plants from fungal diseases.

![Chemical structures](19)

A series of 2-mercaptopyrimidines (20) were screened for their in vitro antibacterial and antifungal activities against Gram-positive organisms (*E. faecalis* and *S. aureus*), Gram-negative organisms (*K. Pneumoniae* and *E. coli*), and fungi (*C. Albicans* and *A. niger*) also compared with the standard drugs ciprofloxacin and fluconazole. The results showed that compounds had significant activity against Gram-positive organisms and moderate activity against the Gram-negative organisms and showed significant antitubercular activity with MIC ranging from 0.8 to 6.25 μg (Hussain et al., 2013). Recently, a series of pyrimidines bearing 1, 3, 4-oxadiazole derivatives were screened for antifungal activity against *Candida albicans*, *Penicillium* spp., and *Aspergillus niger*. It was found to have promising antifungal activity at 10 μg/mL concentration (Andrews et al., 2013).

**Antitubercular activity**

Tuberculosis is an infectious disease caused by several species of Mycobacteria. An increase in *Mycobacterium* tuberculosis strains resistant to first line antimycobacterial drugs such as rifampicin and INH has further worsened the situation. This clearly indicates the need of more effective drugs for the treatment of tuberculosis. Chloropyrimidine (21) derivatives were found to exhibit in vitro antitubercular activity. These derivatives containing aryl, heteroaryl, and alkylthio substituents at position 6 and also alkylthio substituents at position 2 revealed that substitution at positions 6 and 2 has great influence on antitubercular activity.
(Agarwal et al., 2002). N-Phenyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidines-5-carboxamides derivatives were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* and found that 2, 3-dimethylphenyl and 3, 4-dimethyl carbamoyl side chains showed 65% inhibition. The presence of methyl groups on phenyl ring of C-5 side chain with *meta*-substituted 4-phenyl was found to show good activity (Virsodia et al., 2008).

The series dihydropyrazolo [3,4- d] pyrimidine derivatives (22) bearing a phenothiazine nucleus were screened. The compound 4-(4-chlorophenyl)-3-methyl-1-(10 H-phenothiazin-2-yl)-4,5-dihydro- 1H-pyrazolo[3,4-d]pyrimidin-6-amine showed most significant activity against Mycobacterium tuberculosis with minimum inhibitory concentration of 0.02 µg/mL (Siddiqui et al., 2014). 1-(3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(2 mercaptoquinolin-3-yl) azetidin-2-one was examined *in-vitro* for antituberculosis activity against *Mycobacterium tuberculosis* and found to be highly effective. (Chandrashekaraiah et al., 2014).

The preliminary in vitro antituberculosis screening of a series of 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phe-nothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidines 6-thiols with substitutions at second position on the phenyl ring of the pyrazolo[3,4-d]pyrimidine nucleus have emerged as potential compounds endowed with excellent antituberculosis activity (Trivedi et al., 2012).

**Antibiotic activity**

Antibacterial antibiotics can be categorized based on their target specificity: "narrow-spectrum" antibiotics target particular types of bacteria, such as Gram-negative or Gram-positive bacteria, while broad-spectrum antibiotics 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) (23), is active against several staphylococcal infections (Reddick et al., 2001). Gourgetin (24), 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).

Antiviral activity

In recent years, there has been growing interest in the synthesis of pyrimidine derivatives as chemotherapeutic agents against various pathogenic viruses. Several pyrimidine derivatives were recognized to be useful in therapies against Human Immunodeficiency Viruses (HIV), Hepatitis B Viruses (HBV), Herpes Simplex Viruses (HSV) and Influenza Viruses. The virally encoded reverse transcriptase enzyme of HIV provides an important target for the development of anti-AIDS drugs. (Turner et al., 1999).

5-iododeoxyuridine (25) and its derivative like 5-ido-2-deoxyuridine (IDU) have been extensively used for viral infections. 5-Trifluoromethyl-2-deoxyuridine was effective against infections resistant to IDU therapy (De Clercq., 2004). Ara-A 9-b-D-arabinofuranosyl adenine, a relatively new antiviral drug, is effective against herpes infections of eye, brain and skin. It is especially effective against IDU-resistant herpes virus (Kwee et al., 1984). Retrovir (AZT-16) is a potent inhibitor of the in vivo replication and cytopathic effects of HIV and has been approved for use against AIDS (Mitsuya et al., 1985).

Zidovudine which is an analogue of thymidine in which the azido group is substituted at the 3-position of the dideoxyribose moiety is active against RNA tumour viruses (retroviruses).
Zalcitabine (26) is another useful drug and is given in combination with Zidovudine (Mitsuya., 1997).

Pyrimidine derivatives were also tested as inhibitors of Varicella Zoster Virus (VZV). VZV is one of eight herpes viruses known to infect humans and other vertebrates, it commonly causes chicken pox in children and both shingles and post herpetic neuralgia in adults (Steiner et al., 2007). The antiviral properties of Pyrrolo [2,3-d] pyrimidine derivatives against H5N1 virus were tested. The derivative (27, 28) containing dihydronaphtho-, naphtho [2,1-b] thiophene- and thieno [2,3-d] pyrimidine ring systems showed good antiviral activity against H5N1 (Rashad et al., 2010).

Pyrimidine derivatives are also effective in HSV infections. 1-Allyl-3,5-diethyl-6-chlorouracil (29) (Acuracil) was used as a drug for the external treatment of herpes simplex and other viral infections of skin and mucous membranes (Gauni et al., 1969). A series of substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives also show good anti viral activity (Mohamed, et al., 2010b) compared to the standard drug Acyclovir.

**Anticonvulsant activity**

Drugs used in the treatment of epilepsy can be divided into two categories: drugs which are used to abolish seizures called as anticonvulsants, and drugs which are used prophylactically to prevent seizures. The series of nitrophenyl 4, 4, 6 trimethyl, 1 H, 4H pyrimidine 2 thiols (NPTP) (30) were screened for their anticonvulsant activity in mice against maximal electro
shock and metrazol (MET) induced convulsions (Gupta et al., 1994). The pyrimidine analogs show significant anticonvulsant activity.

A series of 2-aminopyrimidine derivatives (31) were also evaluated for anticonvulsant, activity using isoniazid-induced convulsion test, and found to be effective (Valarmathy et al., 2011).

**Analgesic activity**

The substituted thienopyrimidines-4-one (32) (Marylene et al., 1998), thienopyrimido benzothiazole and thienopyrimidobenzo oxazoles were screened for their analgesic and anti-inflammatory activity (Russo et al., 1994). These substituted thieno [2, 3-d] pyrimidine-4(3H)-ones were found to possess good analgesic activity (Ishwaarsinh et al., 2000). The 2-(4-fluorobenzylthio)-n-(substituted phenyl) pyrimidine-4-amines were evaluated for analgesic activity. Some of the derivatives showed good analgesic activity when compared to the standard drug pentazocine (Goudgaon et al., 2014).

The 2-[c]- phenyl- 1H- pyrazolo [3, 4- d] pyrimidin-4-yl) acetohydrazide derivative (33) showed analgesic activity by acetic acid induced writhing test using standard drug diclofenac sodium (Vijaya Raj et al., 2006)

**Antipyretic activity**

The several 2-phenylpyrazolo [1, 5-a] pyrimidines and 4, 7-dihydro-4-methyl-2-phenylpyrazolo [1, 5-a] pyrimidin-7-one were reported to have antipyretic activity (Pirisino et
The anti-inflammatory, analgesic and antipyretic activities of the pyrimidine-3-pyrazolin-5-ones (34) and pyrimidine-1,2,4,5,6,7-3H-hexahydroindazol-3-one hybrids were superior to the potent anti-inflammatory drug, Indomethacin (El-Hawash et al., 2006).

Analytical and antipyretic effects of pyrimidine derivatives of coumarin moiety of 4-(4-(2-amino-6-phenyl-pyrimidin-4-yl)-phenoxy methyl)-6-methyl-chromen-2-one (35) have been investigated (Keri et al., 2010).

**Cardiovascular activity**

The 1, 4-dihydropyridines were found to act by inhibiting the entry of Ca$_2^+$ into the voltage-dependent calcium channels of cardiac and vascular muscle cells. The 1, 4-dihydropyridines are still the largest and most widely studied class of calcium channel blockers. Work in this area has led to the synthesis of several dihydropyridine derivatives, some of which have been successfully introduced as commercial products for the treatment of coronary heart diseases and hypertension, e.g. nifedipine, (36)) and Oroticacid (37).

A series of 2-(Alkylthio)-5, 7-disubstituted-1, 2, 4-triazolo [1, 5-a] pyrimidines have been shown as adenosine cyclic 3', 5'-monophosphate phosphodiesterase inhibitors with a potential as cardiovascular agents (Novinson et al., 1982). Pyrazolopyrimidines and pyrazolo [3, 4-d] pyrimidines (38) derivatives are reported to have pharmacological potential as cardiovascular agents (Guccione et al., 1996).
Antihypertensive Activity
Several pyrimidine ring containing drugs have exhibited antihypertensive activity. Prazosin a quinazoline derivative is a selective $\alpha_1$-adrenergic antagonist [Pfizer, 1970]. Its analogues bunazosin (Hara et al., 2005), terazosin (Meredith et al., 1995) and trimazosin (Honkanen et al., 1983) are potent antihypertensive agents. Another quinazoline derivative of ketanserin (39) (Ganjevoort et al., 2004) having a similar effect is an antagonist of both $\alpha_1$-adrenergic and serotonin-S$_2$ receptors. Its mechanism of action however is still controversial. A triaminopyrimidine derivative, minoxidil (40), whose mechanism of action and therapeutic action are similar to Prazosin, has been introduced in therapy for its additional effects, in the treatment of alopecia, male baldness (Wong et al., 1994).

![Chemical structures](image)

The furo [3, 4-d] pyrimidines-2, 4- dione derivatives, analogues of thienopyrimidines-2, 4- diones (Mery et al., 1989) and thienopyrimidine diones (Russell et al., 1988) were found to have good antihypertensive activity.

Antihistaminic and antiallergic activity
Antihistamine is defined as any histamine antagonist that acts upon the H$_1$ histamine receptor. It has been discovered that these H$_1$-antihistamines are actually inverse agonists at the histamine H$_1$-receptor and are used to treat urticaria, anaphylaxis, asthma and allergic rhinitis (Del Cuvillo et al., 2007). Temelastine (SK & F 93944) (41) is a second generation histamine H$_1$ receptor antagonist. Like other second generation histamine H$_1$ receptor antagonist, temelastine practically does not penetrate the blood brain barriers, thus it does not produce the undesired effects as first generation antihistamines (Brown et al., 1986). Icotidine has therapeutic utility in conditions requiring simultaneous antagonism of histamine at H$_1$ and H$_2$ receptors such as allergy associated with gastric and duodenal ulcers (Ikeda et al., 1996).
Non-steroidal anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a very important clinical use in the treatment of inflammation and various painful conditions such as rheumatoid arthritis, fever, respiratory tract infections and oral cavity lesions. In contrast to opioid analgesics NSAIDs relieves pain without interacting with opioid receptors, reduces elevated body temperature (antipyretic effect), and possess anti-inflammatory property. NSAIDs acts by inhibiting COX-1 (cyclooxygenase-1), where as inhibition of COX-2 leads to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of such type of interactions is the reason for gastrointestinal bleeding as the most serious adverse effect of these drugs. Studies suggest that the presence of hydrazone moiety in some compounds have such a pharmacophoric effect.

Afloqualone (42) (Tani., 1979) has been evaluated as a successful anti-inflammatory agent for patients with lower back pain. Proquazone (43) (Clissold., 1987), a condensed pyrimidin-2-one derivative has been reported to exhibit good NSAID potential.

CNS activity

Barbituric acid (2, 4, 6-trioxohexahydropyrimidine) (44) is the parent compound of a group of important central nervous system (CNS) depressants. Barbituric acid was discovered by the German chemist Adolf von Baeyer (Baeyer. 1864). Although barbituric acid itself is not pharmacologically active more than 2550 barbiturate derivatives (5, 5-disubstituted barbituric acids) and related compounds have been identified and about 50-55 drugs are in clinical use around the world at present. Barbiturates produce a wide spectrum of CNS depressant effects.
from mild sedation to total anaesthesia. They are also effective as anxiolytics, hypnotics, and anticonvulsants. The principal mechanism of action of barbiturates is believed to be their affinity for the gamma-aminobutyric acid (GABAA) receptors, which is the principal inhibitory neurotransmitter in the mammalian CNS (Brunton et al., 2005). Barbital (Veronal®) (45) (R=Et) was discovered in 1903 and marketed in 1904 as sedative and hypnotic (Fischer et al., 1903). Phenobarbital (phenobarbitone, Luminal®) (45) (R=Ph) is extensively used as anticonvulsant worldwide (Kwan et al., 2004). The nature of the substituents at position 5 and 1 greatly influence the potency and duration of the barbiturate derivatives. Allobarbital, aprobarbital, pentobarbital and secobarbital are among the frequently used sedative and hypnotic derivatives (Brunton et al., 2005).

![Chemical structures](44)(45)(46)

A novel series of pyrimidine-4-carboxamides and have been recently identified as potent and selective in vivo antagonists of the human A<sub>2A</sub> receptor, this class of compounds may serve as clinically useful treatments for the relief of the symptoms associated with Parkinson’s disease (Gillespie et al., 2009). A novel series of 3-sulfonyl-pyrazolo[1,5-a]pyrimidines (46) and their 5-HT<sub>6</sub> receptor antagonistic activities were tested, among all 3-(3-chlorophenyl sulfonyl)-5,7-dimethyl-pyrazolo derivative, 3-phenyl sulfonyl-5-methoxy methyl 7-methyl pyrazolo derivative, 3-phenyl sulfonyl-5-methyl-7-methoxy methyl pyrazolo derivatives are the most potent antagonists (Ivachtchenko et al., 2011).

**Antihyperuricemic activity**

Allopurinol (1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-one) (47) is the most commonly used antihyperuricemic agent. Allopurinol is one of the synthetic hydroxypyrazolopyrimidine analogs, is an xanthine oxidase (XO) inhibitor at both oxidized and reduced forms of XO which has been widely used in the therapeutic and clinical management of gout and conditions associated with hyperuricemia as well as related inflammatory diseases (Fields et al., 1996; Pacher et al., 2006).
Allopurinol is rapidly oxidized by XO in vivo to its active metabolite oxypurinol (48), a xanthine analogue, (both isosteres of hypoxanthine and xanthine, respectively), which also inhibits XO.

The effect of pyrimidones compound (49) on serum uric acid levels was evaluated in hyperuricemic rats (Evenas et al., 2014). It was highly effective in reducing serum uric acid levels. Inhibition of xanthine oxidase-catalyzed conversion of xanthine to uric acid by preparation of 3-substituted 7H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones, have a potential as a new class of xanthine oxidase inhibitors. Their inhibitory activities against bovine milk xanthine oxidase in vitro were investigated, and some 4-arylmethylidenehydrazino 1H-pyrazolo[3,4-d]pyrimidin-6(7H)-ones exhibited from several times to several hundred times more potent activities than allopurinol (Nagamatsu et al., 2000).

**CONCLUSION**

In spite of the advances in synthetic organic chemistry which enables the chemist to synthesize thousands of molecules from a template molecule, the discovery of actual drugs is serendipitous. However, pyrimidine derivatives seem to be an exception, since the diverse structures made using this template had a wide variety of biological activities. Pyrimidine nucleus occurs in large number of essential molecules in a cell and hence it is not surprising that using the chemical space available in the parent molecule, diverse bioactive molecules are synthesised. Pyrimidine derivatives will continue to be a source of new drugs to treat the ever increasing burden of diseases.

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