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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.

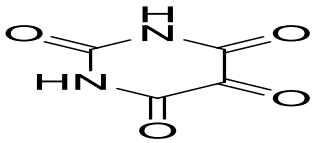
KEYWORDS: Heterocycles, Pyrimidine derivatives, Biological properties, Anticancer, Cardiovascular, CNS, Antimicrobial, Immunological.

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

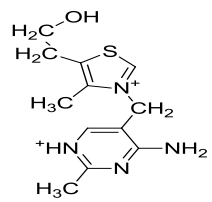
pharmaceuticals, agriculture and industry (Kidwai et al., 2003; Jain et al,. 2006). They find applications in cosmetics, reprography, information storage, plastics, electronics, optics and material sciences (Valverde et al., 2005). Nitrogen, sulfur and oxygen are the most common heteroatoms present in heterocyclic rings. Nitrogen containing heterocycles are the most abundant due to their wide distribution in nucleic acids. The nitrogen congaing heterocyclic compounds in nucleic acids are of two main groups, the purines and pyrimidies. 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).



(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).



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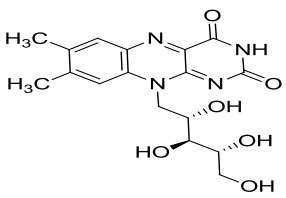

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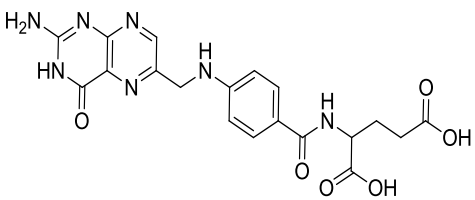


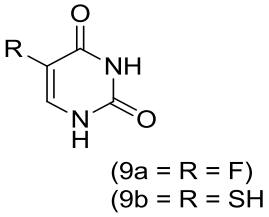
(4)

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 posses 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.



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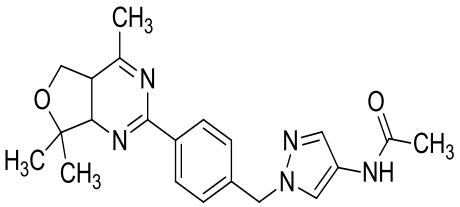

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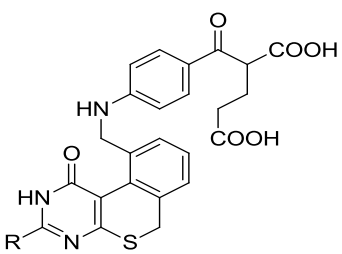
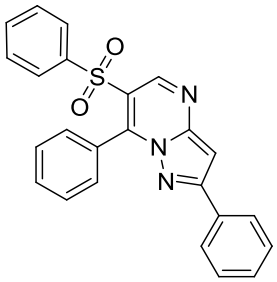


(7)

The pyrazolo [1, 5-*a*] pyrimidines, triazolo [1, 5-*a*] pyrimidines and pyrimido [1, 2-*a*] 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-*a*]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).



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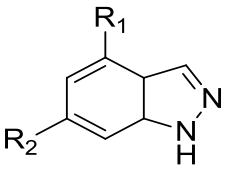
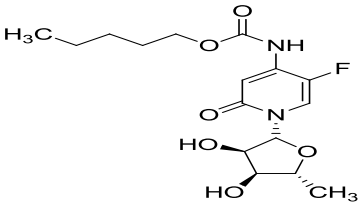


(9)

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).



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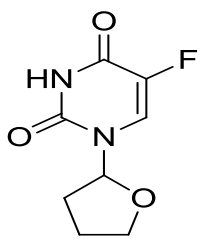
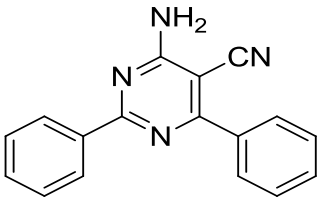


(11)

The pyrido[2,3-d][1,2,4]triozole[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-thiouracile 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).



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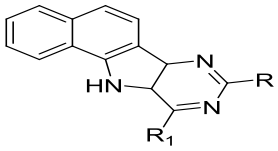


R= CH_3, C_6H_5
R_1= OCH_3, OC_2H_5, NHC_2H_5, NHC_6H_5

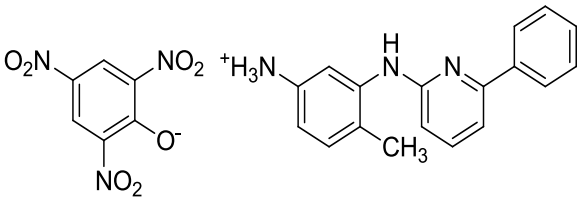
(13)

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-1en-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).



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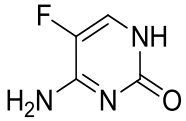
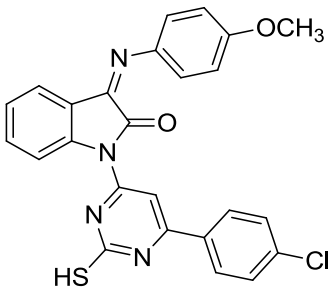


(15)

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*, *Pseudomonasmirabilis*, and *Escherichia coli*. It was found that compounds **(16)** and **(17)** with a methoxy (OCH_3) substitution 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.



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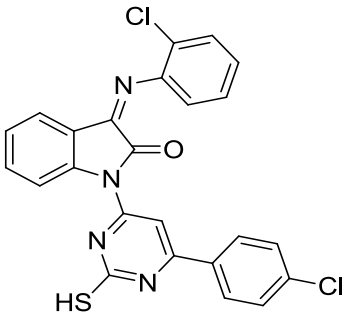

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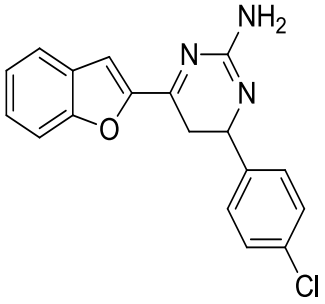
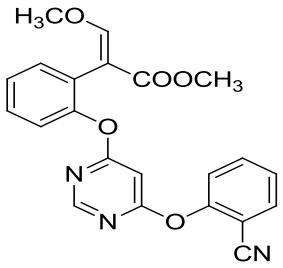


(18)

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). Azoxystrobin (**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.



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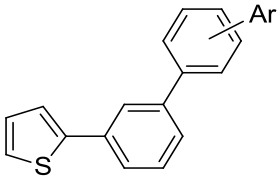


Ar= 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-OCH_3-C_6H_4
3-NO_2-C_6H_4, 4-F-C_6H_4, 2-thienyl

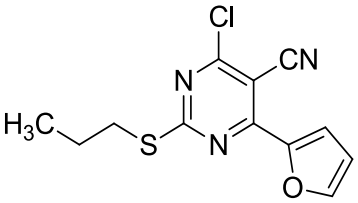
(20)

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 anti mycobacterial 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 carbomyl 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).



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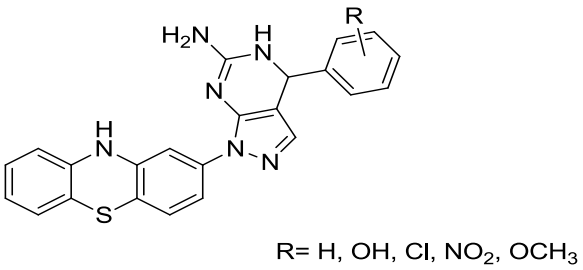


(22)

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).

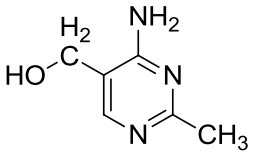
The preliminary in vitro antituberculosis screening of a series of 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phe-nothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidines 6-thiols with substitutions at second position on the phenyl ring of the pyrazolo[3,4-d]pyrimidine nucleus have emerged as potential compounds endowed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



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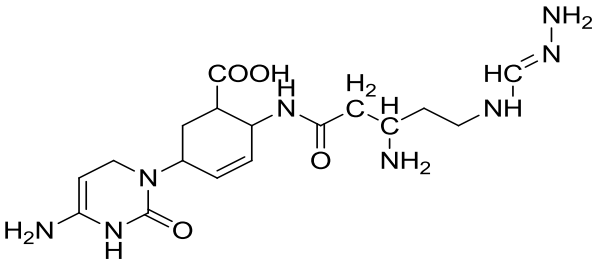


(24)

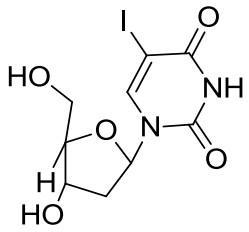
Antiviral activity

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-iodo-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).



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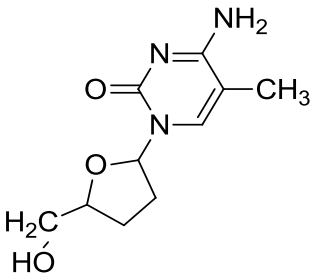
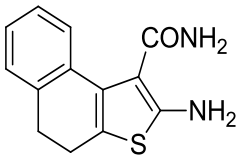


(26)

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).



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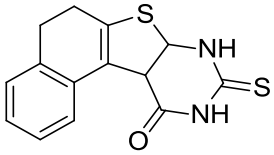

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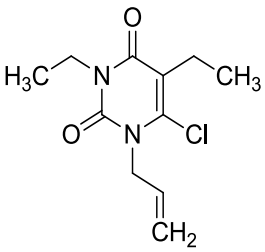


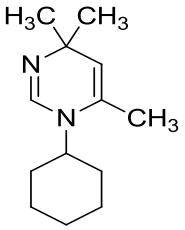
(29)

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.



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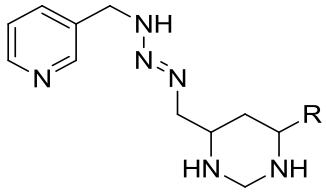
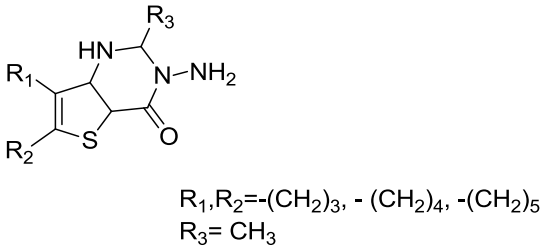


(31)

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).

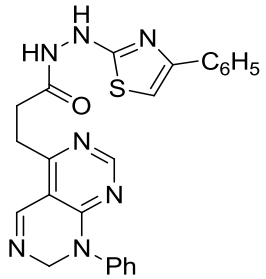
Analgesic activity

The substituted thieno pyrimidines-4-one **(32)** (Marylene et al., 1998), thienopyrimido benzothiazole and thieno pyrimidobenzo 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).



R_1,R_2=-$(CH_2)_3$, - $(CH_2)_4$, -$(CH_2)_5$
R_3= CH_3

(32)



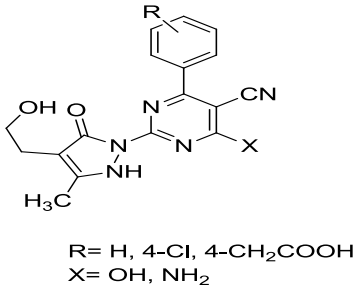
(33)

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 [l, 5-a] pyrimidines and 4, 7-dihydro-4-methyl-2-phenylpyrazolo [l, 5-a] pyrimidin-7-one were reported to have antipyretic activity (Pirisino et

al., 1981). The anti-inflammatory, analgesic and antipyretic activities of the pyrimidine-3-pyrazolin-5-ones (**34)** and pyrimidine-1,2,4,5,6,7-3*H*-hexahydroindazol-3-one hybrids were superior to the potent anti-inflammatory drug, Indomethacin (El-Hawash et al., 2006).



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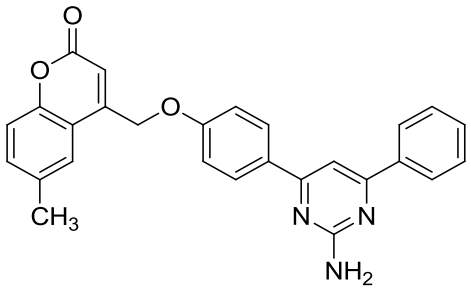
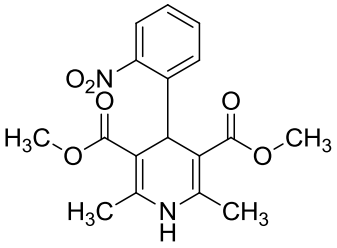


(35)

Analgesic and antipyretic effects of pyrimidine derivatives of coumarin moiety of 4-(4-(2-amino-6-phenyl-pyrimidin-4-yl)-phenoxymethyl)-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)**.



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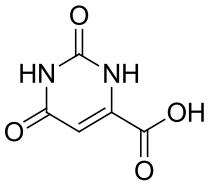

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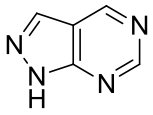
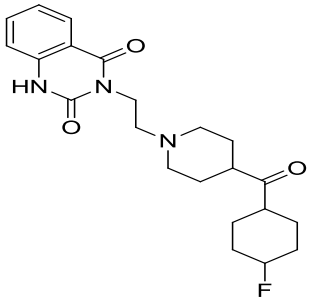


(38)

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 quinozoline derivative is a selective α_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)** (Ganzevoort et al., 2004) having a similar effect is an antagonist of both α1-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).



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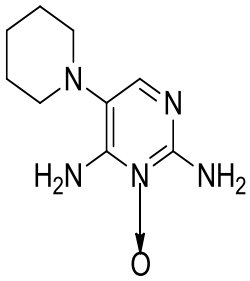
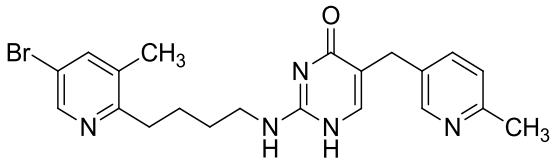


(40)

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

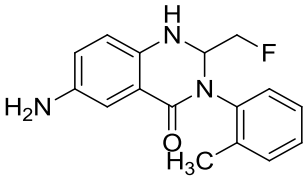
Antihistamine is defined as any histamine antagonist that acts upon the H_1 histamine receptor. It has been discovered that these H_1-antihistamines are actually inverse agonists at the histamine H_1-receptor and are used to treat urticaria, anaphylaxis, asthma and allergic rhinitis (Del Cuvillo et al., 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).



(41)

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.



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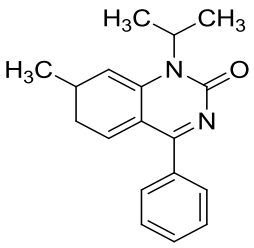


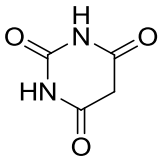
(43)

Afloqualone **(42)** (Tani., 1979) has been evaluated as a successful anti-inflammatory agentfor 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-amino butyric 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).



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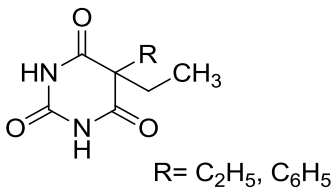

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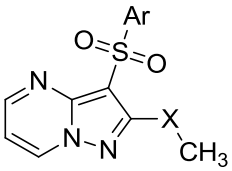
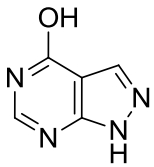


(46)

A novel series of pyrimidine-4-carboxamides and have been recently identified as potent and selective *in vivo* antagonists of the human A_{2A} 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-HT6 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).



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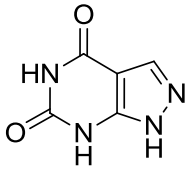

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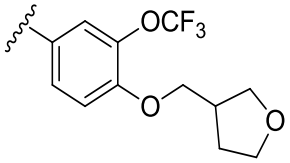

(49)

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.

ACKNOWLEDGEMENT

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REFERENCES

1. Agarwal, N., Srivastava, P., Raghuwanshi, S.K., Upadhyay, D.N., Sinha, S., et al. Chloropyrimidines as a newclass of antimicrobial agents. Bioorg. Med. Chem. 2002; 10: 869-874.
2. Agarwal, O.P., Organic chemistry, Reaction and Reagent. 2006; 735.
3. Al Safarjalani, O.N., Zhou, X.J., Rais R.H., Shi, J., Schinazi, R.F., et al. 5-(Phenylthio)acyclouridine: a powerful enhancer of oral uridine bioavailability: relevance to chemotherapy with 5-fluorouracil and other uridine rescue regimens. Cancer. Chemother. Pharmacol. 2005; 55: 541-551.
4. Andrews, B., Ahmed, M., 2013. Synthesis and characterization of pyrimidine bearing 1,3,4-oxadiazole derivatives and their potential antifungal action. Inter. J.Chem. Stud. 1, 32-39.
5. Baeyer, A., Untersuchungen über die Harnsäuregruppe. Ann. Chem. Pharm., 1864; 131: 291-302.
6. Bailey, S.W., Ayling, J.E., The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc. Natl. Acad. Sci. USA., 2009; 106: 15424-15429.
7. Bano, T., Kumar, N., Dudhe, R., Free radical scavenging properties of pyrimidine derivatives. Org. Med. Chem. Lett., 2012; 2: 34.
8. Barreca, M.L., Chimirri, A., De Luca, L., Monforte, A.M., Monforte, P., et al. Discovery of 2,3-diaryl-1,3-thiazolidin-4-ones as potent anti-HIV-1 agents. Bioorg. Med. Chem. Lett., 2001; 11: 1793-1796.
9. Bettendorff, L., Wirtzfeld, B., Makarchikov, A.F., Mazzucchelli, G., Frédérich, M., et al. Discovery of a natural thiamine adenine nucleotide. Nature. Chem. Biol., 2007; 3: 211-212.
10. Blokhina, N.G., Vozny, E.K., Garin, A.M., Results of treatment of malignant tumors with ftorafur. Cancer., 1972; 30: 390-392.
11. Brown, E.A., Griffiths, R., Harvey, C.A., Owen, D.A., Pharmacological studies with SK&F 93944 (temelastine), a novel histamine HI-receptor antagonist with negligible ability to penetrate the central nervous system. Br. J. Pharmacol., 1986; 87: 569-578.
12. Brunton, L. L., Lazo, J. S., Parker, K. L., Goodman, L. S., Gilman, A. 2005. In Goodman & Gilman's Pharmacological Basis of Therapeutics. McGraw-Hill.

13. Callery, P., Gannett, P., Cancer and Cancer Chemotherapy: In Foye's Principles of Medicinal Chemistry (eds Williams DA and Lemke TL), Lippincott Williams and Wilkins, Philadelphia., 2002; 934-935.
14. Chadwick, B., Addy, M., Walker, D.M., Hexetidine mouthrinse in the management of minor aphthous ulceration and as an adjunct to oral hygiene. Br. Dent. J., 1991; 171: 83-87.
15. Champney, W.S., Bacterial ribosomal subunit synthesis: a novel antibiotic target. Curr. Drug. Targets. Infect. Disord., 2001; 1: 19-36.
16. Chandrashekaraiah, M., Lingappa, M., Vathsala. D., Bhadregowda, D. G., Synthesis of some new pyrimidine-azitidinone analogues and their antioxidant, in vitro antimicrobial, and antitubercular activities. J Chem. 2014: 1-9.
17. Clissold, S.P., Beresford, R., Proquazone. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in rheumatic diseases and pain states. Drugs., 1987; 33: 478-502.
18. Clough, J.M., Godfrey, C.R.A., Azoxystrobin, a novel broad-spectrum systemic fungicide. Pesticide. Outlook., 1996; 7: 16-20.
19. Cohen, F., Bergeron, P., Blackwood, E., Bowman, K.K., Chen, H., et al. Potent, selective, and orally bioavailable inhibitors of mammalian target of rapamycin (mTOR) kinase based on a quaternary substituted dihydrofuropyrimidine. J. Med. Chem., 2011; 54: 3426-3435.
20. De Clercq, E., Antiviral drugs in current clinical use. J. Clin. Viro., 2004; 30: 115-133.
21. Del Cuvillo, A., Sastre, J., Montoro, J., Jauregui, I., Ferrer, M., et al. Use of antihistamines in pediatrics. J. Investig. Allergol. Clin. Immunol. 2007; 17: 28-40.
22. Devegowda, V.N., Kim, J.H., Han, K.C., Yang, E.G., Choo, H., et al., Novel 6-N-arylcarboxamidopyrazolo[4,3-d]pyrimidin-7-one derivatives as potential anti-cancer agents. Bioorg. Med. Chem. Lett., 2010; 20: 1630-1633.
23. Dixon, R.A., and Chopra, I., Polymyxin B and polymyxin B nonapeptide alter cytoplasmic membrane permeability in Escherichia coli. J. Antimicrob. Chemother., 1986; 18: 557-63.
24. Dudhe, R., Sharma, P.K., Verma, P.K., 2015a. Method development of potent pyrimidine derivatives having anticancer, antioxidant and antifungal activity. Int. J. Res. Dev. Pharm. L. Sci., 2015; 4: 1352-1356.
25. El-Hawash, S.A., Badawey, el-S.A., El-Ashmawey, I.M., Nonsteroidal antiinflammatory agents-part 2 antiinflammatory, analgesic and antipyretic activity of some substituted 3-

pyrazolin-5-ones and 1,2,4,5,6,7-3H-hexahydroindazol-3-ones. Eur. J. Med. Chem., 2006; 41: 155-165.

26. El-Nassan, H.B., Synthesis and antitumor activity of novel pyrido[2,3-d][1,2,4]triazole[4,3-a] pyrimidine-5-one derivatives. Eur. J. Med. Chem., 2011; 46: 2031-2036.
27. Eussell, J. A., Carbohydrate metabolism. Annu. Rev. Biochem., 1945; 14: 309-322.
28. Evenas, J., Edfeldt, F., Lepisto, M., Svitacheva, N., Synnergren, A., et al. HTS followed by NMR based counterscreening. Discovery and optimization of pyrimidones as reversible and competitive inhibitors of xanthine oxidase. Bioorg. Med. Chem. Lett., 2014; 24: 1315-1321.
29. Falcao, E.P., de Melo, S.J., Srivastava, R.M., Catanho, M.T., Do Nascimento, S.C., Synthesis and antiinflammatory activity of 4-amino-2-aryl-5-cyano-6-{3- and 4-(N-phthalimidophenyl)}pyrimidines. Eur. J. Med. Chem., 2006; 41: 276-282.
30. Fan, W.Q., Katritzky, A.R., 1,2,3-Triazoles In Comprehensive Heterocyclic Chemistry II. (Eds: Katritzky, A.R., Rees, C.W., E.F.V. Scriven)., Pergamon press: Oxford., 1996; 4: 1-126.
31. Fields, M., Lewis, C.G., Lure, M.D., Allopurinol,an inhibitor of xanthine oxidase, reduces uric acid levels and modifies the signs associated with copper deficiency in rats fed fructose. Free. Radical. Biol. Med., 1996; 20: 595-600.
32. Fischer, E., von Mering, J., Ueber eine neue Klasse von Schlafmitteln. Therap. Gegenw., 1903; 44: 97-101.
33. Fleming, A., On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenza. Br. J. Exp. Pathol., 1929; 10: 226-236.
34. Galmarini, C.M., Mackey, J.R., Dumontet, C., Nucleoside analogues and nucleobases in cancer treatment. Lancet Oncology., 2002; 3: 415-424.
35. Ganzevoort, W., Rep, A., Bonsel, G.J, De Vries, J.I., Wolf, H., Plasma volume and blood pressure regulation in hypertensive pregnancy. J. Hypertens. 2004; 22: 1235-1242.
36. Gauni, K.K., Kohlhage, H., In vitro and in vivo virostatic properties of alkylated pyrimidines against DNA and RNA viruses. Chemotherapy. 1969; 14: 158-169.
37. Gillespie, R.J., Bamford, S.J., Gaur, S., Jordan, A.M., Lerpiniere, J., et al. Antagonists of the human A2A receptor. Part 5: Highly bio-available pyrimidine-4-carboxamides. Bioorg. Med. Chem. Lett. 2009; 19: 2664-2667.

38. Goudar, V., Rashmi, P., Shantharam, U., Hazra, K., Nargund, L.G., synthesis of novel thienopyrimidines and evaluation for their anti-inflammatory activity. J. Chem. Pharm. Res., 2012; 4: 3100-3106.
39. Goudgaon, N.M., Reddy, R.V., Analgesic and anti-inflammatory activities of 2-(4-fluorobenzylthio)-n-(substituted phenyl) Pyrimidine-4-amines. Int. J. Pharm. Chem. Biol. Sci., 2014; 4: 64-68.
40. Guccione, S., Modica, M., Longmore, J., Shaw, D., Barretta, G.U., et al. Synthesis and NK-2 antagonist effect of 1,6-diphenyl-pyrazolo [3,4-d]-thiazolo[3,2-a]4H-pyrimidin-4-one. Bioorg. Med. Chem. Lett. 1996; 6: 59-64.
41. Gupta, A.K., Sanjay, H.P., Kayath, S.A., Sharma, G., Mishra, K.C., Anticonvulsant activity of pyrimidine thiols. Indian. J. Pharmacol., 1994; 26: 227-228.
42. Hara, H., Ichikawa, M., Oku, H., Shimazawa, M., Araie, M., Bunazosin, a selective alpha1-adrenoceptor antagonist, as an anti-glaucoma drug: effects on ocular circulation and retinal neuronal damage. Cardiovasc. Drug Rev., 2005; 23: 43-56.
43. Hilmy, K.M., Elsafty, M.D., Morsy, A.R., Aly, G.M., El-kousy, S.M., Synthesis and Biological Evaluation of pyrrolo [2, 3-d] pyrimidine derivatives as antibacterial and antiviral. J. American. Sci., 2011; 7: 308-314.
44. Honkanen, E., Pippuri, A., Kairisalo, P., Nore, P., Karppanen, H., et al. Synthesis and antihypertensive activity of some new quinazoline derivatives. J. Med. Chem., 1983; 26: 1433-1438.
45. Hussain, M.M.M., Bhat, K.I., Revanasiddappa, B.C., Bharathi, D.R., Synthesis and Biological Evaluation of Some Novel 2-Mercapto Pyrimidines. Inter. J. Pharm. Pharmacl. Sci. 2013; 5: 471-473.
46. Ibraham F.N., Samy A.El.A., Synthesis, reactivity and antitumor activity of some new pyrazolo[3,4-d] pyrimidine and their triazole derivatives. Der. Pharma. Chemica. 2011; 3: 229-238.
47. Ikeda, M., Maruyama, K., Nobuhara, Y., Yamada, Y., Okabe, S., Synthesis and cytoprotective antiulcer activity of 2- and-4-(1H-pyrazol-1yl) pyrimidine derivatives related to mepirizole and dulcerozine. Chem. Pharm. Bull., 1996; 44: 1700-1706.
48. Ishwaarsinh, R.S., Ajay, P.S., Vikas, S.S., Indian. J. Heterocyclic. Chem. 2000; 10: 93.
49. Ivachtchenko, A.V., Golovina, E.S., Kadieva, M.G., Koryakova, A.G., Mitkin, O.D., et al. 2-Substituted 5,6-dimethyl-3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines: new series of highly potent and specific serotonin 5-HT6 receptor antagonists. Eur. J. Med. Chem., 2011; 46: 1189-1197.

50. Jain, K.S., Chitre, T.S., Miniyar, P.B., Kathiravan, M.K., Bendre, V.S., et al. Biological and medicinal significance of pyrimidines. Curr. Sci. 2006; 90: 793-803.
51. Jordi, T.I.B., Grote, T., Schrere, M., Stierl, R., Strathmann, S., et al. Fungicidal mixtures. Canadian. Pat. 2006; 2: 552 240.
52. Keri, R.S., Hosamani, K.M., Shinglapur, R.V., Hugar, M.H., Analgesic,antipyretic and DNA cleavage studies of novel pyrimidine derivatives of coumarin moiety. Eur. J. Med. Chem. 2010; 45: 2597-2605.
53. Kidwai, M., Saxena, S., Rastogi, S., Venkataramanan, R., Pyrimidines as anti-infective agents. Curr. Med. Chem. Anti-Infect Agents. 2003; 2: 269-286.
54. Kumar, B., Kaur, B., Kaur, J., Parmar, A., Anand, R.D., et al. Thermal/microwave assisted synthesis of substituted tetrahydropyrimidines as potent calcium channel blockers. Indian. J. Chem. 2002; 41: 1526-1530.
55. Kumar, D.B.A., Prakash, G.K., Kumaraswamy, M.N., Nandeshwarappa, B.P., Sherigara, B.S., et al. Microwave assisted facile synthesis of amino pyrimidines bearing benzofuran and investigation of their antimicrobial activity. Indian. J. Chem. 2006; 45: 1699-1703.
56. Kumaresan, S., Chandrasekaran, S., Sakthivel, K.M., Guruvayoorappan, C., Israel, V.M., Synthesis, characterization and anti-inflammatory activity of some novel pyrimidin-2-amines on Carrageenan–induced paw edema in balb/c mice. J. Chem. Pharm. Res. 2014; 6: 593.
57. Kwan, P., Brodie, M.J., Phenobarbital for the treatment of epilepsy in the 21st. century: A critical review. Epilepsia, 2004; 45: 1141-1149.
58. Kwee, M.S., Stolk, L.M., Formulation of a stable vidarabine phosphate injection. Pharm. Weekbl. Sci. 1984; 6: 101-104.
59. Lee, H.W., Kim, B.Y., Ahn, J.B., Kang, S.K., Lee, J.H., et al. Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. E. J. Med. Chem. 2005; 40: 862-874.
60. Mallikarjunaswamy, C., Bhadregowda, D.G., Mallesha, L., 2013. Synthesis and antimicrobial activity of pyrimidine salts with chloranilic and picric acids. J. Chem. 2013; 1-5.
61. Marylene, F., Cuong, L.D., Francios, H., Chantal, G., J. Med. Chem. 1998; 23, 45.
62. Meredith, P.A., Scott, P.J., Kelman, A.W., Hughes, D.M., Reid, J.L., Effects of Age on the Pharmacokinetics and Pharmacodynamics of Cardiovascular Drugs: Application of Concentration-Effect Modeling. 3. Trimazosin. Am. J. Ther. 1995; 2: 541-545.

63. Mery P.B., James, Mc.N.J., Joan, K.A., Steve, O.J., Laurence, K.B., et al. Eur. J. Med. Chem. 1989; 24: 627.
64. Mitsuya, H., Weinhold, K.J., Furman, P.A., St Clair, M.H., Lehrman, S.N., et al. 3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. Proc. Natl. Acad. Scie. USA. 1985; 82: 7096-7100.
65. Mitsuya, H., Anti-HIV nucleosides: past, present and future, J. Immunoassay. 1997; 18: 285-287.
66. Mohamed, M.S., Awad, S.M., Sayed, A.I., Synthesis of certain pyrimidine derivatives as antimicrobial agents and anti-inflammatory agents. Molecules. 2010a; 15: 1882-1890.
67. Mohamed, S.F., Flefel, E.M., Amr, Ael-G., Abd El-Shafy, D.N., Anti-HSV-1 activity and mechanism of action of some new synthesized substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives. Eur. J. Med. Chem. 2010b; 45: 1494–1501.
68. Mondal, P., Jana, S., Kanthal, L. K., Synthesis of novel mercapto-pyrimidine and amino-pyrimidine derivatives of indoline-2-one as potential antioxidant & antibacterial agents. The Pharma Research. 2010; 3: 17-26.
69. Nagamatsu, T., Fujita, T., Endo, K., Novel xanthine oxidase inhibitor studies. Part 3.[1] Convenient and general syntheses of 3-substituted 7H-pyrazolo [4,3-e]-1,2,4-triazolo[4,3- c]pyrimidin-5(6H)-ones as a new class of potential xanthine oxidase inhibitors. J. Chem. Soc. Perkin. Trans., 2000; 1: 33-42.
70. Novinson, T., Springer, R.H., O'Brien, D.E., Scholten, M.B., Miller, J.P., et al. 2-(Alkylthio)-1,2,4-triazolo[1,5-a]pyrimidines as adenosine cyclic 3',5'-monophosphate phosphodiesterase inhibitors with potential as new cardiovascular agents. J. Med. Chem., 1982; 25: 420-426.
71. Stanisaw., Some biologically active pyrimidine derivatives are prazosin, quinethazone trimethotrexate, folic acid, riboflavin. Jord. J. Chem. 2009; 4: 1-15.
72. Pacher, P., Nivorozhkin, A., Szabo, C., Therapeutic effects of xanthine oxidase inhibitors: Renaissance half a century after the discovery of allopurinol. Pharmaco. Rev., 2006; 58: 87-114.
73. Padmashali, B., Vaidya, V.P., Vijaya Kumar, M.L., Synthesis and pharmacological evaluation of some naphtho [2, 1-b] furo [3, 2-d] pyrimidines. Indian. J. Hetero. Chem. 2002; 12: 89-94.

74. Pedikian, A.Y., Stroihlein, J., Karlin, D., Bodey, G.P., A comparative study of oral tegafur and intravenous 5-fluorouracil in patients with metastatic colorectal cancers. Am. J. Clin. Oncol. 1983; 6: 181-186.
75. Pfizer., US Patent. 1970; 3: 511- 836.
76. Pirisino, R., Mangano, G., Ceppatelli, P., Corrias, M., Ignesti, G., et al. Further investigations on the antinflammatory activity of some 2-phenylpyrazolol [1,5-a]pyrimidine compounds. Farmaco. Sci. 1981; 36: 682-91.
77. Ram, V.J., Haque, N., Guru, P.Y., Chemotherapeutic agents XXV: synthesis and leishmanicidal activity of carbazolylpyrim- idines. E. J. Med. Chem. 1992; 27: 851-855.
78. Rashad, A.E., Heikal, O.A., El-Nezhawy, A.O.H., Abdel-Megeid F.M.E., Synthesis and isomerization of thienotriazolopyrimidine and thienotetrazolo pyrimidine derivatives with potential anti-inflammatory activity. Heteroatom. Chem. 2005; 16: 226-234.
79. Rashad, A.E., Shamroukh, A. H , Abdel-Megeid, R. E., Mostafa, A., El-shesheny, R., et al. Synthesis and screening of some novel fused thiophene and thienopyrimidine derivatives for anti-avian influenza virus (H5N1) activity. Eur. J. Med. Chem. 2010; 45: 5251-5257.
80. Reddick, J.J., Saha, S., Lee, J., Melnick, J.S., Perkins, J., et al. The mechanism of action of bacimethrin, a naturally occurring thiamin antimetabolite. Bioorg. Medi. Chem Lett. 2001; 11: 2245-2248.
81. Russell, R.K., Press, J.B., Rampulla, R.A., McNally, J.J., Falotico, R., et al. Thiophene systems. 9. Thienopyrimidinedione derivatives as potential antihypertensive agents. J. Med. Chem. 1988; 31: 1786-1793.
82. Russo, F., Romeo, G., Santagati, N.A., Caruso, A., Cutuli, V., et al. Synthesis of new thienopyrimidobenzothiazoles and thienopyrimidobenzoxazoles with analgesic and antiinflammatory properties. Eur. J. Med. Chem. 1994; 29: 569-578.
83. Shaaban, M.R., Saleh, T.S., Mayhoub, A.S., Farag, A.M., Single step synthesis of new fused pyrimidine derivatives and their evaluation as potent Aurora-A kinase inhibitors. Eur. J. Med. Chem. 2011; 46: 3690-3695.
84. Siddiqui, A. B., Trivedi, A. R., Kataria, V.B., Shah, V.H., 4,5-Dihydro-1H-pyrazolo[3,4-d]pyrimidine containing phenothiazines as antitubercular agents. Bioorg. Med. Chem. Lett. 2014; 24: 1493-1495.
85. Singh, P., Kumar, R., Sharma, B. K., Quantitative structureactivity relationship study of 5-iodo- and diaryl-analogues of tubercidin: inhibitors of adenosine kinase. J. E. I. Medi. Chem. 2003; 18: 395-402.

86. Sirisoma, N., Kasibhatla, S., Nguyen, B., Pervin, A., Wang, Y., et al. Discovery of substituted 4-anilino-2-(2-pyridyl)pyrimidines as a new series of apoptosis inducers using a cell- and caspase-based high throughput screening assay. Part 1: Structure–activity relationships of the 4-anilino group. Bioorg. Med. Chem. 2006; 14: 7761-7773.
87. Smith, J., Andes, D., Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamic considerations. Ther. Drug. Monit. 2008; 30: 167-172.
88. Steiner, I., Kennedy, P.G., Pachner, A.R., The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet. Neurol. 2007; 6: 1015-1028.
89. Tani, J., Yamada, Y., Oine, T., Ochiai, T., Ishida, R., et al. Studies on biologically active halogenated compounds. 1. Synthesis and central nervous system depressant activity of 2-(fluoromethyl)-3-aryl-4(3H)-quinazolinone derivatives. J. Med. Chem. 1979; 22: 95-9.
90. Trivedi, A.R., Dholariya, B.H., Vakhariya, C.P., Dodiya, D.K., Ram, H.K., et al. Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-d]pyrimidine derivatives. Med. Chem. Res. 2012; 21: 1887-1891.
91. Turner, B.G., Summers, M.F., Structural biology of HIV. J. Mol. Biol. 1999; 285: 1-32.
92. Valarmathy, J., Joshua, L.S., Senthilkumar, K.L., Synthesis of 2-aminopyrimidine derivatives and evaluation for anti tubercular, anti-convulant and anti-inflammatory activity. Univ. Int. J. Chem. 2011; 2: 61-68.
93. Valverde, M.G., Torroba, T., Sulfur-Nitrogen Heterocycles. Molecules. 2005; 10: 318-320.
94. Vijaya Raj, K.K., Naryana, B., Ashalatha, B.V., Suchetha Kumari, N., New Thiazoles Containing Pyrazolopyrimidine Moiety as Possible Analgesic Agents. J. Pharmacol. Toxicol. 2006; 6: 559-565.
95. Virsodia, V., Pissurlenkar, R.R., Manvar, D., Dholakia, C., Adlakha, P., et al., Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted N-phenyl-6-methyl-2-oxo-4 phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides. Eur. J. Med. Chem. 2008; 43: 2103-2115.
96. Wong, W.M., Seifert, L., Minoxidil use in female alopecia. Ann. Pharmacother. 1994; 28: 890-891.
97. Yano, S., Kazuno, H., Sato, T., Suzuki, N., Emura, T., et al. Synthesis and evaluation of 6-methylene-bridged uracil derivatives. Part 2: Optimization of inhibitors of human thymidine phosphorylase and their selectivity with uridine phosphorylase. Bioorg. Med. Chem., 2004; 12: 3443-3450.

98. Zempleni, J., Galloway, J.R., McCormick, D.B., Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans. Am. J. Clin. Nutr., 1996; 63: 54-66.