Exploration of the Chemistry and Biological Properties of Pyrimidine as a Privilege Pharmacophore in Therapeutics

Olayinka O. Ajani, Jessica T. Isaac, Taiwo F. Owoeye and Anuoluwa A. Akinsiku
Department of Chemistry, Covenant University, CST, Canaanland, Km 10 Idiroko Road, P.M.B. 1023, Ota, Ogun State, Nigeria

Corresponding Author: Olayinka O. Ajani, Department of Chemistry, Covenant University, CST, Canaanland, Km 10 Idiroko Road, P.M.B. 1023, Ota, Ogun State, Nigeria  Tel: +2348061670254

ABSTRACT

The pyrimidine moiety is one of the most widespread heterocycles in biologically occurring compounds, such as nucleic acids components (uracil, thymine and cytosine) and vitamin B1. Due to its prebiotic nature to living cells in biodiversity, it is an highly privileged motif for the development of molecules of biological and pharmaceutical interest. This present work deals with the exploration of chemistry and medicinal diversity of pyrimidine which might pave way to long await discovery in therapeutic medicine for future drug design.

Key words: Nitrogen heterocycle, biological activity, pyrimidine, anticancer, drug design

INTRODUCTION

Over the years, the heterocyclic compounds have attracted numerous attentions due to their wide applications in medicinal chemistry research. Nitrogen-containing heterocyclic compounds have been prominent even in early studies of chemistry. Heterocyclic compounds are cyclic compounds with at least two different elements as ring members’ atoms, the commonest atoms include nitrogen, oxygen and sulphur (Lagoja, 2005). Heterocycles are in abundance in nature and are very significant in our lives because of their existence in many naturally occurring molecules such as hormones, antibiotics, caffeine etc. (Nagaraj and Reddy, 2007). The pyrimidine ring is a heterocyclic aromatic compound that occurs widely in nature. Pyrimidines are one of the two most important biological families of nitrogen containing molecules called nitrogen bases. Pyrimidines have been known since their early days as essential components of nucleic acid to their current usage in the chemotherapy of AIDS (Jain et al., 2006).

Furthermore, the prebiotic synthesis of nucleic acid bases is a central issue in the RNA-world hypothesis, one of the main proposals for the origin of life, based on the self-assembly of nucleic acid monomers (Ruiz-Mirazo et al., 2014). Possible scenarios for the synthesis of nucleic acids are still under debate and despite the abiotic synthesis of several nucleobases, the relevance of these syntheses to the origin of life is not well established (Kakiya et al., 2002). Pyrimidine core is found as the inner skeleton in the nucleic acid components; uracil, thymine and cytosine. Pyrimidine template and its heterofused derivatives exhibit promising anticoagulant (Saif, 2005), antitubercular (Trivedi et al., 2008), antileukemic (Liu et al., 2003), antimicrobial (Moustafa et al., 2007), anti-inflammatory (Panda and Chowdary, 2008), anti-HIV (Meng et al., 2014), analgesic (Abdelazeem et al., 2014), anticancer (Antonelli et al., 2014), antitumoral (Barlaam et al., 2014), anticonvulsant (Paronikyan et al., 2007), antiplatelet (Giordanetto et al., 2014), antifungal...
Int. J. Biol. Chem., 2015

(Faty et al., 2015), antiviral (Danesh et al., 2015), antibacterial (Andrews and Ahmed, 2015), antimalarial (Manohar et al., 2012) and antinociceptive (Bookser et al., 2005) activities. The group of pyrido[1,2-a] pyrimidin-4-ones is a well-known class of aza-bridgehead fused heterocyclic compounds which have miscellaneous pharmaceutical applications (Katritzky et al., 2004).

The successful application of pyrimidine derivatives in many ways, their utility in applied chemistry and in more fundamental and theoretical studies has made the literature of the subject to be correspondingly vast (Katzung, 1995). In view of the occurrence of microorganisms resistance to drugs currently in use and the continuous outbreak of new infectious diseases every time, there is a continuous need for the exploration of new heterocyclic compounds which are pyrimidine-based as potential agents of wide therapeutic implications for effective drug design. This study was undertaken to provide recent advances in the general assessment of pyrimidine and its wide range of uses both in chemistry and pharmacy. The specific objectives are to: Expound on the historical review into the world of pyrimidine, highlight major synthetic pathways of valuable pyrimidine derivatives, explore recent advances in chemistry of pyrimidine for effective drug design, critically review various biological activities of pyrimidine in recent time and draw attention of researchers into the beneficial role of pyrimidine in fighting diseases.

Natural occurrence: Pyrimidine is a core skeleton which serves as constituent of natural biologically active compounds (Lagoja, 2005). Pyrimidine occurs naturally in substances such as vitamins like thiamine, riboflavin (found in milk, egg and liver), folic acid (from liver and yeast), barbituric acid (2,4,6-trihydroxy pyrimidine), nucleic acids components (uracil, cytosine and thymine), coenzymes, purines, pterins, nucleotides, alkaloids obtained from tea, coffee, cocoa and essential components of many drug molecules (Gupta et al., 2010). Vicine may be the first simple pyrimidine derivative found to occur in nature. It was discovered in 1870 in Vetch seeds (Vicia sativa, Vicia faba L.) by Ritthausen. Of the nucleic acid pyrimidines, uracil and dihydrouracil, isolated from beef spleen, have been found in free form (Lagoja, 2005). A number of related pyrimidines also occur in lesser amounts in certain nucleic acids (Wade, 1999). Other pyrimidines of general natural occurrence are orotic acid and thiamine (vitamin B1) (Farlex Inc., 2015).

Physical properties: Pyrimidine is a colorless compound. It is a crystalline solid with melting point of 22°C which dissolves in water to give a neutral solution and reacts with mineral acids to form salts. It’s molecular formula is C4H4N2 with molar mass 80.088 g cm⁻³ and boiling point of 123-124°C. By X-ray diffraction, pyrimidine dimensions of the carbon-carbon distances are (1.35-1.40 Å), they are similar to benzene with the bond length of 1.40Å (Verma et al., 2012).

CHEMISTRY

Chemical properties: Six membered heterocyclic compounds are π-deficient when substituted by electronegative groups or additional nitrogen atom. The 2-, 4- and 6- positions on the pyrimidine ring are naturally electron deficient because of the strong electron-pulling effect of the ring nitrogen atoms which are much more electronegative than carbon. The 5-position is not as electron-deficient as 2-, 4- or 6- position, though it can be made so by the general inductive effect. On the 5-position, electrophilic reagents attack under certain conditions. For example nitration, nitrosation and halogenation can easily take place here (Brown, 2009).
Structure of pyrimidine: Pyrimidine has one axis of symmetry along 2, 5-axis as shown in Fig. 1, but the symmetry is lost upon unequal substitution at 4- and 6-positions. It is π-deficient because of the presence of electronegative N-atoms. Consequently, the electron densities at 2- and 4/6-positions are depleted and these positions become strongly electron loving and are herein referred to as the electrophilic positions. The electron density at 5-position is only slightly depleted; hence the ring therefore retains benzenoid properties at this position, which herein referred to as the benzenoid position (Woodgate et al., 1987). However, the electron density at the N-atoms is greatly enhanced and the N-atoms constitute the basic and the nucleophilic centers in pyrimidine. It has three difference pairs of bond length and four different bond angles.

Dipole moments of pyrimidine: Pyrimidine is considered to be polar in nature with an experimentally determined dipole moment ranging between 2.1 and 2.4 D. The theoretically calculated value lied between 2.13 and 2.25 D. This showed a good correlation with the experimentally determined values (Undheim and Benneche, 1996).

Ionization properties: Pyrimidine in its monoprotonated and diprotonated state has basic pKₐ of 1.3 and -6.9, respectively, which compares with value of 5.2 for pyridine. The very marked lowering of basicity observed in pyrimidine is attributed to the electronegativity of the second ring nitrogen. Electron-releasing substituents will counteract the electron deficiency of the ring and thereby increase the basicity (Undheim and Benneche, 1996). The pKₐ values of pyrimidine derivatives had also been documented in both basic and acidic media. The basic pKₐ values for 2 (1H)-pyrimidinone, 4 (3H)-pyrimidinone and 5-hydroxypyrimidine, which structures are shown in Fig. 2, are 2.2, 1.7, 1.8, while their acidic pKₐ values were 9.2, 8.6 and 6.8, respectively. An extensive compilation and tabulation of acidic and basic pKₐ values for simple pyrimidines in water at 20-25°C has been published (Undheim and Benneche, 1996; Kappe, 1994).

Synthesis of pyrimidine

Synthesis via [3+3] cycloaddition: Preparation of pyrimidines is done generally by condensation reaction between a three-carbon compound and compounds having the amidine structure with sodium hydroxide or ethoxide as a catalyst (Rao et al., 2013). The reaction can be illustrated by the condensation of acetamidine with ethyl acetoacetate, as shown in Fig. 3, to form 2,6-dimethylpyrimidin-4-ol (Rao et al., 2013).

Fig. 1: Structure of un-substituted pyrimidine showing its one plane of symmetry

Fig. 2: Structural attribute showing pKa of protonated and non-protonated pyrimidines
Synthesis by reaction of 1,3-dielectrophilic component: Preparation of pyrimidine derivative by the reaction of 1,3-dielectrophilic component with urea derivative in the presence of K$_2$CO$_3$ was achieved under reflux as shown in Fig. 4. Tert-butanol was reported as the suitable solvent for this reaction (Kim et al., 2007).

Synthesis via intramolecular cyclization initiated by decarboxylation: Decarboxylation of malic acid with concentrated sulfuric acid formed β-ketoacid which subsequently reacted with urea to produce pyrimidine via chlorination and hydrogenation processes. This involves an initial decarboxylation of malic acid under the influence of concentrated H$_2$SO$_4$ to afford a β-ketoacid intermediate which upon reaction with urea gave a 2,4-dione (Fig. 5). This was treated with PdCl$_3$ to produce 4-chloropyrimidine (uracil) which finally undergoes reduction with H$_2$/Pd to eventually give the unsubstituted pyrimidine in good yield as shown in Fig. 5 (Rao et al., 2013).

Synthesis from condensation of amidine-containing substrate: A common method for the preparation of the fully aromatized pyrimidine skeleton is the condensation of amidine-containing substrates with suitable carbonyl compounds. Among these protocols, α,β-unsaturated carbonyl and 1,3-dicarbonyl compounds are often used. For example, in the search for COX-2-selective inhibitors, Almansa and co-workers synthesized a variety of pyrazolo[1,5-a] pyrimidines by condensing 4,5-disubstituted pyrazole with an array of enones or with 1,3-dicarbonyl derivatives with the pathway shown in Fig. 6 (Almansa et al., 2001).
Fig. 6: Synthesis of pyrazolo[1,5-a] pyrimidines from amidine

Fig. 7: Synthesis of 4-amino-5-cyano-2-methyl pyrimidine

Fig. 8: Synthesis of pyrimido[1,2-a] benzimidazole from allenic nitrile

Fig. 9: Solvent-free green approach to dihydropyrimido[4,5-d] pyrimidine

Synthesis through condensation of malononitrile: According to a review by Gupta et al. (2010), condensation of malononitrile with amide-bearing group such as formamide or benzamidine has been reported to result in the formation of 4-amino-5-cyano pyrimidine via a versatile intermediate which was presented in the Fig. 7.

Synthesis from benzimidazole derivatives: Asobo and co-workers reported a novel synthesis of biologically active pyrimido[1,2-a] benzimidazole from 2-aminobenzimidazole and allenic nitrile in good yields according to equimolar stoichiometry shown in Fig. 8. Some of these heterocycles showed modest antibiotic and antiarrhythmic properties (Asobo et al., 2001).

Green synthetic approach to pyrimidine: Based on Fig. 9, a green and solvent-free three-component condensation of 6-[(dimethylamino)methyleneamino]uracil, an aldehyde and NH₄OAc in the presence of HOAc afforded a one-pot synthesis of dihydropyrimido[4,5-d] pyrimidine when heated under reflux (Prajapati et al., 2007).
Preparation from chalcone precursor: Reaction of chalcone with thiourea and guanidine hydrochloride in the presence of sodium hydroxide formed the 4,6-disubstituted pyrimidin-2-thiol and 2 amino-4,6-disubstituted pyrimidines respectively as shown in Fig. 10 (Udupi et al., 2005).

Pyrimidine synthesis by cyclo-condensation from dithioacetal: Pyrimidine-5-carboxaldehydes were obtained from cyclo-condensation reaction of α-formylaroylketene dithioacetal with guanidine or benzamidine (Scheme 9), which in turn was obtained from formylation of α-oxoketene dithioacetal with DMF in the presence of POCl₃ in basic medium (Mathews and Asokan, 2007). The detail is as pictorially described in Fig. 11.

Synthesis from heterogeneous catalytic approach: Silica Supported Sulfuric Acid (SSA) was used as an efficient heterogeneous catalyst in the research efforts of Ajani et al. (2011), for the reaction of α, β-unsaturated carbonyl (chalcones) with urea to afford substituted mono and bicyclic pyrimidin-2(1H)-ones in good to excellent yields as shown in the Fig. 12. They established the efficiency of SSA through its re-usability and higher yields with short reaction times than those obtained from conventional refluxing in concentrated hydrochloric acid (HCl).

Synthesis of monastrol via utilization of Lewis acid promoter, Yb(OTf)₃: There has been some interest in monastrol, a potentially important chemotherapeutic for cancer which acts as an inhibitor of mitotic kinesin. For instance, Kappe (1994) successfully synthesized racemic monastrol using microwave mediation in 60% yield from 3-hydroxybenzaldehyde, ethyl acetoacetate and thiourea in the presence of PPE. However, Dondoni et al. (2002) improved the synthesis by using Yb(OTf)₃ as the Lewis acid promoter in THF under conventional heating by reflux, as shown in Fig. 13, to produce monatrol in 95% yield.

Glycosidic residual synthesis of pyrimidine: Sugar residue can be a subunit in the aldehyde, 1,3-dicarbonyl, or urea; consequently, substitution of the dihydropyrimidine (DHPM) ring may occur in one of three places depending on which component originally contains the glycosidic

Fig. 10: Preparation of 4,6-diphenylpyrimidine from chalcone

Fig. 11: Preparation of pyrimidine-5-carboxaldehydes from dithioacetal
Fig. 12: SSA-assisted catalytic synthesis of pyrimidine derivatives

Fig. 13: Microwave-assisted synthesis of monastrol in excellent yield

Fig. 14: Lewis acid synthesis of 1,2,3,4-tetrahydropyrimidine-5-carboxylate residue (Dondoni et al., 2001). From the example presented in Fig. 14, hydropyran carbaldehyde was utilized to deliver 1,2,3,4-tetrahydropyrimidine-5-carboxylate derivative as the major product with moderate diastereo-selection (Dondoni et al., 2001).

Synthesis of pyrimidine by Biginelli reaction: In addition to modification of the catalyst, several variants of the Biginelli reaction have emerged as viable alternatives. However, each method requires pre-formation of intermediates that are normally formed in the one-pot Biginelli reaction. First, Atwal et al. (1989) reported the reaction between aldol adducts with urea or thiourea in the presence of sodium bicarbonate in dimethyl formamide at 70°C to give 1,4-dihydro pyrimidines. 1,2,3,4-tetrahydropyrimidine was then produced by deprotection of 1,4-dihydropyrimidines (Fig. 15). In some other cases, the reaction can be catalyzed by Lewis acids such as boron trifluoride (Selvam et al., 2012).
Synthesis by electrophilic activation of amide: According to Fig. 16, benzo-fused pyrimidine derivative, 4-cyclohexyl-6-methoxy-2-phenylquinazoline was prepared by the reaction of certain amides, N-(4-methoxyphenyl) benzamide with carbonitriles (cyclohexanecarbonitrile), under electrophilic activation of the amide with 2-chloropyridine and trifluoromethanesulfonic. For the quantitative yield to be obtained, the reaction must be carried out at a controlled temperature of between -78°C and >45°C in the presence of dichloromethane (Movassagi and Hill, 2006).

Synthesis by catalytic cyclization of β-formyl enamide: A novel and efficient synthesis of pyrimidine from β-formyl enamide involved samarium chloride catalysed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation (Fig. 17). This procedure is highly efficient for the synthesis of 2,5,6-trisubstituted pyrimidine (Barthakur et al., 2007).

Synthesis by cross coupling reaction: Karpov and Muller (2003) reported the coupling of acid chlorides with terminal alkynes using one equivalent of triethylamine under Sonogashira conditions. They expatiated that subsequent addition of amines or amidinium salts to the intermediate alkynones formed, allowed a straightforward access to enaminones and pyrimidines under mild conditions shown in Fig. 18 and in excellent yields (Karpov and Muller, 2003).
Preparation via sodium salt of propanol derivatives: Reaction of sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol with different amidinium salts resulted in 2-substituted pyrimidine-5-carboxylic esters by heating under reflux for 1 h in the presence of dimethylformamide (DMF) at a carefully controlled temperature of 100°C as shown in Fig. 19 (Gupta et al., 2010).

Prebiotic synthesis of pyrimidine: The isolation of purine and pyrimidine from Murchison meteorite was cited as evidence that these substances might have been present in a prebiotic environment. The first prebiotic synthesis of pyrimidine was the synthesis of cytosine from prop-2-ynenitrile (cyanoacetylene) and cyanate as shown in the Fig. 20 (Lagoja, 2005).

Microwave-assisted synthesis: An efficient one-pot synthetic method for the highly substituted 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives was accomplished via microwave irradiation. Microwave-assisted Multi-Component Reaction (MCR) of benzaldehyde, 5-phenyl-1,3,4-thiadiazole-2-amine and ethyl acetoacetate in acetic acid without any catalyst afforded ethyl7-methyl-2,5-diphenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate in 85% yield (Fig. 21) (Zhao et al., 2014).

Synthesis via 1-benzotriazolyl-2-propynones: A novel 1-benzotriazolyl-2-propynones provided access to the fused ring systems of pyrido[1,2-a]pyrimidin-2-ones and 2H-quinolizin-2-ones, known
for their diverse biological activities. Reactions of N-(phenylpropioyl)benzotriazole with substituted 2-aminopyridines afforded pyrido[1,2-α] pyrimidin-2-ones in good yields (71-73%) and the by-product yield was drastically reduced when the reaction was carried out in sealed tube for 12 h as shown in Fig. 22 (Katritzky et al., 2004).

**Synthesis via steroidal ketone:** The preparation of steroid/nonsteroid fused 7-substituted pyrazolo[1,5-α]pyrimidines is described by a one-pot reaction of steroidal/nonsteroidal ketones, aromatic aldehydes and 3-amino-1H-pyrazoles/5-amino-1H-pyrazoles in the presence of potassium tert-butoxide. When anisaldehyde and 3-aminopyrazole were used, steroidal fused 7-substituted pyrazolo[1,5-α]pyrimidine was obtained in 76% as shown in Fig. 23 (Saikia et al., 2014).

**Synthesis via ring transformation of pyran-3-carbonitrile derivatives:** Synthesis of tricyclic pyrimidine chemosensor, BTP-1 was achieved by using a mild base through ring transformation of suitably functionalized 4-(methylthio)-2-oxo-6-naphthyl-2H-pyran-3-carbonitriles with 2-aminobenzothiazole in DMF using DBU as the base as shown in Fig. 24 (Nandre et al., 2014).

**Ice bath synthesis of pyrimidine:** Recent discovery showed that the synthesis of pyrimidines under a methane/nitrogen atmosphere is possible with high yields if a urea source is present. In this process, the presence of frozen water or ice is a decisive factor. With water subjected to freeze-thaw cycles, the synthesis of pyrimidines and triazines is strongly favored in ice cold condition. The ice matrix plays the role of a protective medium that avoids the degradation of molecules such as the pyrimidines, enhances the yields and diminishes the side reactions, which constitute the constraints for the actual prebiotic relevance of cyanoacetylene, acetylene, or urea (Menor-Salvan et al., 2009).

Fig. 22: Synthesis of pyrido[1,2-α] pyrimidin-2-ones from 2-propynone synthon

Fig. 23: Synthesis of steroid-fused 7-substituted pyrazolo[1,5-α]pyrimidines
Reactions of pyrimidine derivatives

Acylation reaction at nitrogen: Acylation of the ring nitrogen in fully conjugated pyrimidine derivatives led to a pyridimium salt as reported by Cruickshank et al. (1984). This is achieved by treatment of pyrimidine with ethanoyl chloride in the presence of mineral acid (Fig. 25). In similar manner, benzoylation of uracil in the presence of pyridine gives 1-benzoyluracil provided there is limited supply of benzoyl chloride and 1,3-dibenzoyluracil in excess of benzoylating agent as shown in Fig. 25 (Cruickshank et al., 1984). Selective removal of 1-benzoyl group can be effected under mild basic condition to furnish the 3-benzoyl derivatives (Cruickshank et al., 1984).

Alkylation reaction at nitrogen: Reactions of electrophiles with annular nitrogen have been reported. Simple alkylations of pyrimidines with non-tautomerizable substituents were largely controlled by steric factors. For instance, 4-t-butyl-6-methylpyrimidine with benzyl chloride in toluene formed exclusively 1-benzylated product as presented in Fig. 26 (Curphey and Prasad, 1972).

Oxidation at nitrogen: Pyrimidines and methylpyrimidines are susceptible to decomposition, ring-carbon oxidation and ring-opening reactions on direct N-oxidation, resulting in low yields of N-oxides. Activating substituents are required. According to Fig. 27, with m-chloroper benzoic acid in chloroform, pyrimidine afforded pyrimidine N-oxides in 48% yield whereas when 2-methyl pyrimidine was used as the starting material 2-methyl pyrimidine N-oxides product was obtained in 55% yield as reported by Undheim and Benneche (1996).
Fig. 26: Alklylation reaction of pyrimidine derivatives at the nitrogen

\[
\text{H}_2\text{C} - \text{CH}_3 + \begin{array}{c} \text{Br} \\ \text{Toluene} \end{array} \rightarrow \text{HC}_3\text{CH}_2 \quad \text{1-benzylated product}
\]

Fig. 27: Oxidation reaction of 2-substituted pyrimidine at the nitrogen

\[
\begin{array}{c} \text{Nitration at the carbon:} \\ \text{Pyrimidine and its cation are highly } \pi \text{-deficient and resist nitration. The } \pi \text{-system in the 5-nitro derivative is further electron-depleted. Presumably adducts are formed which either are oxidized or ring-opened. Nitration of pyrimidine is a very difficult task. However, aryl substituted pyrimidine are often nitrated preferentially at the aryl. According to Fig. 28, nitration of 4-phenyl pyrimidine in the presence of a mixture of concentrated nitric and sulphuric acids yielded 40 and 60% of 4-o-nitrophenylpyrimidine and 4-m-nitrophenyl pyrimidine, respectively (Bourguignon et al., 1982).} \\ \text{Nitrosation at carbon:} \\ \text{Nitrosation takes place in the benzenoid 5-position in pyrimidines with three strongly electron-donating groups e.g. oxo, thioxo, or amino groups. In disubstituted pyrimidines, the relative positions of the substituents are decisive for any reaction. According to Fig. 29a-b, 4,6-diamino- and 4,6-dihydroxypyrimidines are 5-nitrosated to give 5-nitrosopyrimidine-4,6-diamine and 5-nitrosopyrimidine-4,6-diol respectively whereas their 2,4-isomers fail to react as shown in Fig. 29c-d. Nitrosation is brought about by nitrous acid or by nitrite esters (Brown et al., 1994).} \\ \text{Alkoxylation and aryloxylation at carbon:} \\ \text{Nucleophilic displacement of 2- and 4/6-halo substituents by alkoxy or aryloxy ions occurred readily except in the presence of strongly electron-releasing substituents in the ring (Undheim and Bennche, 1996). In 2-bromo-4-chloro-5-ethoxypyrimidine, the chlorine in the more reactive 4-position was selectively substituted during ethanolysis to give 2-bromo-4,5-diethoxypyrimidine as shown in Fig. 30a. Whereas, in the}
\end{array}
\]
Fig. 29(a-d): Nitrosation reaction of pyrimidine derivatives at the carbon

Fig. 30(a-b): Alkoxylation and aryloxylation reactions of pyrimidine derivatives at the carbon

Fig. 31: Diazo coupling reaction of 4-amino-2-hydroxypyrimidine

2,4,5-trifluoro-6-iodopyrimidine, it was the fluorine in the 4-position which suffered preferential methanolation to form the 2,5-difluoro-4-ido-6-methoxypyrimidine as given in Fig. 30b (Undheim and Benneche, 1996).

**Diazo coupling reaction of pyrimidine**: The diazonium electrophile is weak and requires highly nucleophilic counterparts for reaction. At least, two strong electron-releasing substituents at C2 and C4 (or C6) are needed for pyrimidines to couple at C5. For example, according to Fig. 31, reaction of 4-amino-2-hydroxypyrimidine with diazonium salt afforded azo dye, 4-amino-5-(phenyldiazenyl) pyrimidin-2-ol in good yield as reported by Brown *et al.* (1994).

**Halogenation reaction of pyrimidine**: Pyrimidines are halogenated directly by electrophilic reagents in the 5-position. Halogenations in the electrophilic positions are by nucleophilic exchange reactions. Pyrimidine needs to be activated, for example by electron donating group such as a hydroxyl or amino group or 2-tertbutyl, for chlorination to occur in the 5-position. Some of the suitable chlorinating agents that have been used include chlorine in the presence of base; phenyl iododichloride, sulfuryl chloride or thionyl chloride with ferric chloride as catalyst. According to Fig. 31a, the treatment of 4-amino-2-hydroxypyrimidine with sulfuryl chloride in the presence of ferric chloride afforded 4-amino-5-chloro-2-hydroxypyrimidine (Undheim and Benneche, 1996). However, 4-amino-5-bromo-2-hydroxypyrimidine is formed in 71-78% yield using bromine in solvents like benzene or nitrobenzene (Undheim and Benneche, 1996) as shown in Fig. 32b.
**Int. J. Biol. Chem., 2015**

![Chemical structures](image)

Fig. 32(a-b): Halogenation reaction of 4-amino-2-hydroxypyrimidine

![Chemical reaction](image)

Fig. 33: Reduction reaction of un-substituted pyrimidine

![Chemical reaction](image)

Fig. 34: Oxidation reaction of 2-substituted pyrimidine

**Reduction of pyrimidine:** The reduction of pyrimidine by NaB(CN)H₃ in methanol, with concurrent trapping of the reduced forms by benzyl chloroformate, was reported to give the dibenzyl pyrimidine-1,3(2H,4H)-dicarboxylate called the pyrimidine enamine (Undheim and Benneche, 1996) as shown in Fig. 33.

**Oxidation of pyrimidine:** The 2-methyl group side chain of pyrimidine was oxidized to carboxyl group by oxidizing agents such as potassium permanganate in order to obtain pyrimidine-2-carboxylic acid as shown in Fig. 34. A 5-methyl group was difficult to oxidize and an N-methyl group was resistant. Under mild oxidizing conditions, pyrimidine carbaldehydes were formed (Undheim and Benneche, 1996).

**Synthetic applications of pyrimidine derivatives:** Some interesting non-medical applications were found once again for pyrimidines. The first successful prebiotic-related synthesis of a pyrimidine nucleoside from a free base and a non-activated sugar was reported when it was found that drying and heating 2-pyrimidinone and ribose gave the corresponding β-furanosyl ribonucleoside, which structure is shown in Fig. 35, in about a 12% yield (Bean et al., 2007). The synthesis and spectroluminescent properties of new 4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidinium styryls as fluorescent dyes for bimolecular detection were reported (Balanda et al., 2007). In the presence of RNA, these dyes significantly enhanced emission intensity and might become RNA-specific fluorescent probes.

The nucleophilic substitution reaction of manganocene, Cp₂Mn, with an equimolar amount of the Li⁺ salt of 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (hppH), with the structure presented in Fig. 35, affords the neutral dimer [CpMn(hpp)₂], further substitution of the Cp ligands has been found to give the unusual dimeric manganese cage compound [LiMn(hpp)₃]₂ via dimerization of a trisorganomanganate monomer. A series of biodegradable polymers containing...
the anticancer prodrug 5-fluorouracil and 4-amino-N-(2-pyrimidinyl) benzenesulfonamide, shown in Fig. 35, were prepared by first condensing chlorinated poly (lactic acid) or chlorinated poly(lactic acid-coglycolic acid) with potassium sulfadiazine and then with 1,3-dihydroxyethyl-5-fluorouracil (Chang et al., 2007). A one-pot synthesis of 1-benzoyl-2(S)-substituted-5-iodo-2,3-dihydro pyrimidin-4(1H)-ones was developed, based on the tandem decarboxylation b-iodination of 6-carboxyhexahydropyrimidin-4-one and these were processed further to give α-substituted b-amino acids with high enantioselectivity like (a-c) (Diaz-Sanchez et al., 2007).

1,3-Dimethyl-5-{(thien-2-yl)-[4-(1-piperidyl)phenyl]methylene}-(1H,3H)-pyrimidine-2,4,6-trione, shown in Fig. 36 which is a new merocyanine dye, was synthesized from 1,3-dimethylbarbituric acid and its solvatochromic response in 26 solvents of different polarity was measured (El-Sayed and Spange, 2007). The adsorption of α-amino acid/5-nitroso-6-oxopyrimidine conjugates onto activated carbon increased its adsorption capacity for Cu²⁺ as established by Gutierrez-Valero et al. (2007). Furthermore, the 2-oxo- and 2-thioxopyrimidines (Fig. 36) were prepared in a one-pot cyclocondensation of β-ketoester, aldehyde and urea/thiourea using BnNEt₃Cl as catalyst and under solvent-free conditions (Mobinikhaledi et al., 2007). Similarly, a successful protocol for the hydrogenation of 4,6-diamino-1H-pyrimidine-2-thione to 4,6-diamino-3,4-dihydro-1H-pyrimidine-2-thione has been reported in zinc dust in the presence of adequate amount of glacial acetic acid (Sayed et al., 2006).

**BIOLOGICAL ACTIVITIES**

**Antibacterial activity:** Andrews and Ahmed (2015) reported 5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(4-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one to be the most promising antibacterial among the series screened by them. 2-(1,3-benzothiazol-2-ylimino)-1,2-dihydro pyrimidine-4,6-diamine excellent activity on both gram positive and negative isolate (Soliman et al., 2014). Other
pyrimidines harvested in literatures as probable antibacterial agents include 5-benzoyl-6-phenylpyrimidin-2-one (Gulcan et al., 2014), pyrimidine-nucleotide (cGMP-AM) (Beckert et al., 2014), pyrrolidinyl-pyrimidine (Nguyen et al., 2014) and 5-amino-thiazolo[4,5-d]pyrimidine (Jang et al., 2011) as shown in Fig. 37.

Antifungal activity: Flucytosine is a pyrimidine-based drug used as an antifungal agent for the treatment of extreme infections like candida and cryptococcus while hexitidine is used to treat primarily aphthous ulceration (Jain et al., 2006). Efficient antifungal activity of 2-amino-4-methoxy-6-substituted thiazolyl pyrimidine reported (Rindhe et al., 2005). Pyrimidine has largest zones of inhibition against Aspergillus niger (10 mm) and Penicillium sp. (9 mm) among the compounds screened by Faty et al. (2015). Benzothiazole-pyrimidine was the most active among those tested by Maddila et al. (2013). According to the structure shown in Fig. 38, pyrrolo[2,3-d]pyrimidines possessed excellent activity against Candida albicans with MIC 0.31-0.62 mg mL$^{-1}$ (Hilmy et al., 2010) (Fig. 2).
Antiviral activity: Recently, pyrimidine-based compounds and derivatives have a wide interest due to their useful antiviral properties. 5-iododeoxyuridine is pyrimidine-based heterocyclic antiviral agents that have been used extensively for the treatment of viral infections (Jain et al., 2006). 2-(4-methyl-5-nitro-6-(pyrrolidin-1-yl)-pyrimidin-2-ylamino)-3-phenylpropanoic acid (Fig. 39) exhibited antiviral activity with IC$_{50}$ of 73 μg mL$^{-1}$ (Danesh et al., 2015) while 2,4-diaminopyrimidine derivative (IC$_{50}$ = 13 μg mL$^{-1}$) was the most effective among the series screened by Fernandez-Cureses et al. (2015). Other recently reported pyrimidines with promising antiviral activities in Fig. 39, were 7-(4-methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e] [1,2,4]-triazolo[1,5-c]pyrimidine-2-thione (Mohamed et al., 2015a) and 5-(5-(sec-butythio)-1,3,4-thiadiazol-2yl)-2-methylpyrimidin-4-amine (Wu et al., 2015) (Fig. 3).

Anticancer activity: Tarceva is a pyrimidine-based cancer drug available in the market. 1,2,3,4-tetra hydropyrimidine analogue was found to be potent against various human cancer cell lines (Bari et al., 2015). Triazolo-pyrimidinone (Mohamed et al., 2015b) and pyrazolo-pyrimidine (Pogorelcnik et al., 2015) with the structures shown in Fig. 40, revealed promising anticancer activities compared to the activity of the commonly used anticancer drug, doxorubicin in both MCF-7 and A549 cell lines. 4-(2-chlorophenyl)-6-(2,4-dichlorophenyl)pyrimidin-2-amine exhibited remarkable growth inhibition at single dose (10 μM) against lung cancer cell line HOP-92 (Rashid et al., 2014). 2-[(5-anilino-1,3,4-thiadiazol-2-yl)methyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine-4(3H)-one was reported to show improved activity against lung and breast cancer (Mavrova et al., 2014) (Fig. 40).

Antitubercular activity: Tuberculosis is an infectious disease that is caused by the bacterium *Mycobacterium tuberculosis*. Capreomycin and viomycin, shown in Fig. 41, are commercially available pyrimidine-containing antitubercular drugs (Jain et al., 2006). Deazapurine nucleoside (IC$_{50}$ = 0.0012±0.0001 μM) was reported to be highly potent antitubercular pyrimidine (Malnuit et al., 2015). Imidazo[1,2-c]pyrimidin-4-ol emerged as the most potent among the series screened by Barot et al. (2014) against *M. tuberculosis* H$_{37}$Rv. According to Shakya et al. (2012),

Antiviral activity: Recently, pyrimidine-based compounds and derivatives have a wide interest due to their useful antiviral properties. 5-iododeoxyuridine is pyrimidine-based heterocyclic antiviral agents that have been used extensively for the treatment of viral infections (Jain et al., 2006). 2-(4-methyl-5-nitro-6-(pyrrolidin-1-yl)-pyrimidin-2-ylamino)-3-phenylpropanoic acid (Fig. 39) exhibited antiviral activity with IC$_{50}$ of 73 μg mL$^{-1}$ (Danesh et al., 2015) while 2,4-diaminopyrimidine derivative (IC$_{50}$ = 13 μg mL$^{-1}$) was the most effective among the series screened by Fernandez-Cureses et al. (2015). Other recently reported pyrimidines with promising antiviral activities in Fig. 39, were 7-(4-methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e] [1,2,4]-triazolo[1,5-c]pyrimidine-2-thione (Mohamed et al., 2015a) and 5-(5-(sec-butythio)-1,3,4-thiadiazol-2yl)-2-methylpyrimidin-4-amine (Wu et al., 2015) (Fig. 3).

Anticancer activity: Tarceva is a pyrimidine-based cancer drug available in the market. 1,2,3,4-tetra hydropyrimidine analogue was found to be potent against various human cancer cell lines (Bari et al., 2015). Triazolo-pyrimidinone (Mohamed et al., 2015b) and pyrazolo-pyrimidine (Pogorelcnik et al., 2015) with the structures shown in Fig. 40, revealed promising anticancer activities compared to the activity of the commonly used anticancer drug, doxorubicin in both MCF-7 and A549 cell lines. 4-(2-chlorophenyl)-6-(2,4-dichlorophenyl)pyrimidin-2-amine exhibited remarkable growth inhibition at single dose (10 μM) against lung cancer cell line HOP-92 (Rashid et al., 2014). 2-[(5-anilino-1,3,4-thiadiazol-2-yl)methyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine-4(3H)-one was reported to show improved activity against lung and breast cancer (Mavrova et al., 2014) (Fig. 40).

Antitubercular activity: Tuberculosis is an infectious disease that is caused by the bacterium *Mycobacterium tuberculosis*. Capreomycin and viomycin, shown in Fig. 41, are commercially available pyrimidine-containing antitubercular drugs (Jain et al., 2006). Deazapurine nucleoside (IC$_{50}$ = 0.0012±0.0001 μM) was reported to be highly potent antitubercular pyrimidine (Malnuit et al., 2015). Imidazo[1,2-c]pyrimidin-4-ol emerged as the most potent among the series screened by Barot et al. (2014) against *M. tuberculosis* H$_{37}$Rv. According to Shakya et al. (2012),
Fig. 40: Selected pyrimidine moieties with anticancer activity

Fig. 41: Selected pyrimidine moieties with antitubercular activity

1-(β-D-arabinofuranosyl)-4-thio-5-hydroxymethyluracil, showed in Fig. 41, was the most active with MIC₅₀ = 0.5 μg mL⁻¹. N-(2-fluoro-4-(furan-2-yl)-6-(4-methoxybenzylamino)pyrimidin-5-yl)formamide inhibited the growth of M. tb H₃⁷Rv at ICₙ₀ < 0.2 μg mL⁻¹ and also exhibited low toxicity towards mammalian cells as reported by Read et al. (2010).

**Antitumor activity:** Pyrrolo[2,3-d]pyrimidines with folate receptor was identified by Wang et al. (2015) as potential antitumor compound. Abbas et al. (2015) reported 4-(4-fluorophenyl)-6-oxo-2-[(1-
Int. J. Biol. Chem., 2015

Fig. 42: Selected pyrimidine moieties with antitumor activity

henyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]-1,6-dihydropyrimidine-5-carbonitrile, showed in Fig. 42, to be promising antitumor because it exhibited also high inhibition (91%) against EGFR-TK. 2-(5-cyano-2-(prop-2-yn-1-ylthio))-6-(3,4,5-trimethoxyphenyl)-pyrimidin-4-yl) hydrazine carbothioamide showed marked inhibition of cell migration and in vivo tumor suppressing and antimetastasis (Ma et al., 2015). 1-(4-chlorophenyl)-3-(4-((3-(diethylamino)propyl)amino)thieno[3,2-d]pyrimidin-2-yl)phenyl)urea showed antitumor activities with IC50 values of 0.081 μM, 0.058 μM, 0.18 μM and 0.23 μM against H460, HT-29, MKN-45 and MDA-MB-231 cell lines (Liu et al., 2014a) (Fig. 42).

Analgesic and anti-inflammatory activity: 2-[Chloro-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl]acetohydrazide, screened via acetic acid induced writhing test, showed good analgesic activity (Raj et al., 2006). 1-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-2-((pyrimidin-2-ylthio)methyl)-1H-benzo[d] imidazole showed in Fig. 43, was a selective COX-2 inhibitor with IC50 8.2 mM as well as promising anti-inflammatory agent (68.4%) while 1-((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)-2-(pyrimidin-2-ylthio)methyl)-1H-benzo[d]imidazole has dual action as anticancer and anti-inflammatory pyrimidine (Rathore et al., 2014). According to Sharma et al. (2014), N-(4-hydroxy-6-tosyl)-5,6,7,8-tetrahydropryrido[4,3-d]pyrimidin-2-yl)-4-nitrobenzamide (IC50 = 254 μM) and N-(4-hydroxy-6-tosyl-5,6,7,8-tetrahydropryrido[4,3-d]pyrimidin-2-yl)isonicotin amide (IC50 = 231 μM) exhibited good analgesic and anti-inflammatory profiles and proved effective in the treatment of neuropathic pain. 5-(2-(Azepan-1-yl)ethyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one showed in Fig. 43, was reported to be more active than ketorolac standard drug, hence, cloud be developed into anti-inflammatory/analgesic drug with the probability of fewer side effects (Abdelazeem et al., 2014) (Fig. 7).

Antimalarial activity: N,N′-(4,4′-(Furan-2,5-diyl)bis(3,5-diisopropoxy-4,1-phenylene))dipyrimidine-2-carboxim idamide with structure in Fig. 44, showed good activity against P. falciparum at IC50 of 8.5 nM (Liu et al., 2014b). Pyrimidine-based anti-malarial drugs available in the market include perimethamine, sulfadiazine and trimethoprim. However, more efforts have been developed in antimalarial drug research because of drug resistance problem. Thus, hybrids of 4-aminoquinoline, N1-(7-chloroquinolin-4-yl)-N2-(4-(piperidin-1-yl)pyrimidin-2-yl)propane-1,3-diamine screened by Singh et al. (2014) and N1-(7-chloroquinolin-4-yl)-N2-(6-methyl-
2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)ethane-1,2-diamine reported by Manohar et al. (2012) showed antiplasmodial activity in nM range against chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum* (Fig. 44).

**Anti-HIV activity:** The Human Immunodeficiency Virus (HIV) is a virus that attacks the immune system. 4-((4-((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl) benzenesulfonamide (Fang et al., 2015) and 3,4-dihydro-2H,6H-
Fig. 45: Selected pyrimidine moieties with anti-HIV activity

pyrimido[1,2-c][1,3]benzothiazin-6-imine (Ghebremariam et al., 2014) as well as 3,4-dihydro-2H-benzo[4,5]isothiazolo[2,3-a]pyrimidine (Okazaki et al., 2015a), shown in Fig. 45, exhibited strong HIV-1 inhibitory potency at EC_{50} of 3.22, 0.30 and 0.29 μM, respectively. Chemical transformation of this isothiazolo- was achieved later to produce 2-(2-mercaptophenyl)-1,4,5,6-tetrahydropyrimidine (Fig. 45) which was unveiled as an active anti-HIV moiety with promising feature (Okazaki et al., 2015b). 4-((7-(Mesitylamino)-[1,2,4]triazolo[1,5-a]pyrimidin-5-yl)amino)benzonitrile was discovered as potent HIV-1 NNRTIs using a structure-guided core-refining approach (Wang et al., 2014). Other promising anti-HIV pyrimidine established through research efforts include 2-(4-cyanophenylamino)-4-(2-cyanovinylphenylhydrazonomethyl)pyrimidine (Meng et al., 2014) and 4-(7-(mesityloxy)pyrazolo[1,5-a]pyrimidin-5-ylamino)benzonitrile (Tian et al., 2014) which structures were shown in Fig. 45.

**Antiplatelet activity:** Current anti-platelet drugs are important for the prevention and treatment of acute ischemic syndromes. Discovery of N-(2-hydroxyethyl)-N-methyl-2-morpholino-4-oxo-9-(1-phenoxymethyl)-4H-pyrido[1,2-a]pyrimidine-7-carboxamide shown in Fig. 46, as oral PI3Kb inhibitors which was useful as antiplatelet agent was reported by Giordanetto et al. (2014). Efforts by Okuda et al. (2014a, b) on collagen-induced platelet aggregation revealed 2-(4-methoxy phenyl)-4-chloro-5,6-dihydro[1]benzothiepino[5,4-d]pyrimidine (Okuda et al., 2014a) and 2-phenyl-4-ethylamino-5,6-dihydro[1]benzoxepino[5,4-d]pyrimidine (Okuda et al., 2014b) presented in Fig. 46, as promising anti-platelet candidates with potencies superior to aspirin.

**Kinase inhibitory activity:** 2-(4-methoxyphenyl)-5-methyl-N-(4-methylphenyl)[1,3]oxazolo[5,4-d]pyrimidin-7-amine strongly inhibited VEGFR-2 kinase and HUVEC with IC_{50} values of 0.33 and 0.29 μM (Deng et al., 2015). (R)-5-chloro-N^2-[4-(4-methylpiperazin-1-yl)phenyl]-N^1-[tetrahydrofuran-2-yl]methyl)pyrimidine-2,4-diamine presented in Fig. 47, was developed as novel ACK1/TNK2 inhibitors using a fragment-based approach (Lawrence et al., 2015). 1-(2-(4-bromo phenyl)-2-chloroethyl)-N-(2-chlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine showed in
Fig. 46: Selected pyrimidine moieties with antiplatelet activity

Fig. 47: Selected pyrimidine moieties with kinase inhibitory activity

Fig. 48: Selected pyrimidine moieties with antitamoebic activity

Fig. 47, was reported as a SRC family kinase inhibitor which could be a feasible approach for glioblastoma treatment (Ceccherini et al., 2015).

Antiamoebic activity: Amoebiasis, the most aggressive disease of the human intestine, is caused by the anaerobic protozoan parasite Entamoeba histolytica (Lejeune et al., 2009). Out of sixteen compounds evaluated against HM1: IMSS strain of Entamoeba histolytica by Parveen et al. (2010), 4-(4-chlorophenyl)-6-ferrocenyl-2-piperidin-1-yl-pyrimidine with the structure showed in Fig. 48, was found most active and least toxic among all the compounds. From the in silico molecular docking simulation investigated by Yadava et al. (2015), 1-(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-ylsulfonyl)-N-p-tolylmethanamide (IC$_{50}$ = 0.68 μg mL$^{-1}$), represented in Fig. 48, was found to be more efficient than the metronidazole drug standard (IC$_{50}$ = 1.80 μg mL$^{-1}$) against the same Entamoeba histolytica.
Central nervous system depressant activity: Chronic anxiety and epilepsy are common and serious disorder of Central Nervous System (CNS). The CNS depressant agents are an important class of drugs, which are useful in the treatment of anxiety and related emotional disorders. A series of tetracyclic pyrimidines were screened for CNS depressant, skeletal muscle relaxant and anticonvulsant activities in Swiss albino mice (Thore et al., 2015). The result showed that 1-isopropyl-4-(4-methylphenyl)-6,7,8,9-tetrahydro[1,2,4]triazolo[4,3-a]benzo(b)thieno[3,2-e]pyrimidine-5(4H)-one, 4-(4-methylphenyl)-1-pyrrolidin-1-ylmethyl-6,7,8,9-tetrahydro[1,2,4]triazolo[4,3-a]benzo(b)thieno[3,2-e]pyrimidine-5(4H)-one and 4-(4-methylphenyl)-1-piperidin-1-ylmethyl-6,7,8,9-tetrahydro[1,2,4]triazolo[4,3-a]benzo(b)thieno[3,2-e]pyrimidine-5(4H)-one with the presented structures in Fig. 49, exhibited promising activities, which are comparable to the standard (Thore et al., 2015).

Herbicidal activity: Assay of a series of pyrimidine scaffolds designed by Cheng et al. (2015) for herbicidal activities revealed that 5-(4-chloro-2-fluoro-5-(prop-2-yn-1-yl oxy)phenyl)-1,7-dimethyl-1H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, with the structure shown in Fig. 50, exhibited significant herbicidal efficacy. 2-methyl-4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-6-(prop-2-yn-1-yl oxy)pyrimidine exhibited excellent inhibition activities against weed root growth (Ma et al., 2014a). Most of the pyrimidines synthesized by Ma et al. (2014b) expressed bleaching activities with 4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-6-(prop-2-yn-1-yloxy)pyrimidine, presented in Fig. 50, showing the best bleaching activity to gramineous weeds. It produced the highest inhibition of chlorophyll level in seedlings of Pennisetum alopecuroides L.
CONCLUSION

The synthetic utility of pyrimidines as precursors and valuable intermediates for the successful design of diverse biologically active compounds has given impetus to these studies. Owing to widespread application of pyrimidine in medicinal chemistry research and its occurrence in many biological entities valuable to life, tremendous amount of literature have been accumulated and documented over the years. We have herein reviewed recent advances in the chemistry and biology of pyrimidine in order to provide valuable information on how this scaffold could be used to develop new drugs and bioactive motifs for effective fight against drug resistance which is an emerging bottleneck in pharmaceutical research.

REFERENCES

Abbas, S.E.S., E.I. Aly, F.M. Awadallah and W.R. Mahmoud, 2015. 4-substituted-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine derivatives: Design, synthesis, antitumor and EGFR tyrosine kinase inhibitory activity. Chem. Biol. Drug Des., 85: 608-622.

Abdelazeem, A.H., S.A. Abdelatief, M.T. El-Saadi, H.A. Omar and S.I. Khan et al., 2014. Novel pyrazolopyrimidine derivatives targeting COXs and iNOS enzymes; design, synthesis and biological evaluation as potential anti-inflammatory agents. Eur. J. Pharm. Sci., 62: 197-211.

Ajani, O.O., R.I. Ituen and A. Falomo, 2011. Facile synthesis and characterization of substituted pyrimidin-2(1H)-ones and their chalcone precursors. Pak. J. Sci. Ind. Res., 54: 59-67.

Almansa, C., A.F. de Arribas, F.L. Cavalcanti, L.A. Gomez and A. Miralles et al., 2001. Synthesis and SAR of a new series of COX-2-selective inhibitors: Pyrazolo[1,5-a]pyrimidines. J. Med. Chem., 44: 350-361.

Andrews, B. and M. Ahmed, 2015. An efficient synthesis, characterization and anti-bacterial activity of pyrimidine bearing 1,3,4-thiadiazole derivatives. Indian J. Chem., 54B: 406-411.

Antonelli, A., G. Bocci, C. La Motta, S.M. Ferrari and P. Fallahi et al., 2014. CLM29, a multi-target pyrazolopyrimidine derivative, has anti-neoplastic activity in medullary thyroid cancer in vitro and in vivo. Mol. Cell. Endocrinol., 393: 56-64.

Asobo, P.F., H. Wahe, J.T. Mbafor, A.E. Nkengfack, Z.T. Fomum, E.F. Sophue and D. Dopp, 2001. Heterocycles of biological importance. Part 5. 1 The formation of novel biologically active pyrimido [1, 2-a] benzimidazoles from allenic nitriles and aminobenzimidazoles. J. Chem. Soc. Perkin Trans., 1: 457-461.

Atwal, K.S., G.C. Rovnyak, B.C. O'Reilly and J. Schwartz, 1989. Substituted 1,4-dihydropyrimidines. 3. Synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidines. J. Org. Chem., 54: 5898-5907.

Balanda, A.O., K.D. Volkova, V.B. Kovalska, M.Y. Losytskyy, V.P. Tokar, V.M. Prokopets and S.M. Yarmoluk, 2007. Synthesis and spectral-luminescent studies of novel 4-oxo-4,6,7,8-tetrahydropyrrolol[1,2-a]thieno[2,3-d]pyrimidinium styryls as fluorescent dyes for biomolecules detection. Dyes Pigments, 75: 25-31.

Bari, A., M.K. Parvez, A.A. Khan, A.M. Alanazi, S.A. Syed, M.S. Al-Dosari and A.M. Alobaid, 2015. A facile one-pot synthesis and anticancer evaluation of novel substituted 1,2-dihydropyridine and 1,2,3,4-tetrahydropyrimidine analogues. J. Heterocycl. Chem. 10.1002/jhet.2400

Barlaam, B., S. Cosulich, S. Degorce, M. Fitzek and F. Giordanetto et al., 2014. Discovery of 9-(1-anilinoethyl)-2-morpholino-4-oxo-pyrido [1, 2-a] pyrimidine-7-carboxamides as PI3K/δ inhibitors for the treatment of PTEN-deficient tumours. Bioorg. Med. Chem. Lett., 24: 3928-3935.
Barot, K.P., S.V. Jain, N. Gupta, L. Kremer and S. Singh et al., 2014. Design, synthesis and docking studies of some novel (R)-2-(4-chlorophenyl)-3-(4-nitrophenyl)-1, 2, 3, 5-tetrahydrobenzo [4, 5] imidazo [1, 2-c] pyrimidin-4-ol derivatives as antitubercular agents. Eur. J. Med. Chem., 83: 245-255.

Barthakur, M.G., M. Borthakur, P. Devi, C.J. Saikia and A. Saikia et al., 2007. A novel and efficient lewis acid catalysed preparation of pyrimidines: Microwave-promoted reaction of urea and β-formyl enamides. Synlett, 2: 223-226.

Bean, H.D., Y. Sheng, J.P. Collins, F.A. Anet, J. Leszczynski and N.V. Hud, 2007. Formation of a β-pyrimidine nucleoside by a free pyrimidine base and ribose in a plausible prebiotic reaction. J. Am. Chem. Soc., 129: 9556-9557.

Beckert, U., M. Grundmann, S. Wolter, F. Schwede and H. Rehmann et al., 2014. cNMP-AMs mimic and dissect bacterial nucleotidyl cyclase toxin effects. Biochem. Biophys. Res. Commun., 451: 497-502.

Bookser, B.C., B.G. Ugarkar, M.C. Matelich, R.H. Lemus and M. Allan et al., 2005. Adenosine kinase inhibitors. 6. Synthesis, water solubility and antinociceptive activity of 5-phenyl-7-(5-deoxy-β-d-ribofuranosyl)pyrrolo[2,3-d]pyrimidines Substituted at C4 with glycaminides and related compounds. J. Med. Chem., 48: 7808-7820.

Bourguignon, J., S. Chapelle, P. Granger and E.G. Queguiner, 1982. Study of the reactivity of thienyldiazines: Nitration and 13C nuclear magnetic resonance in concentrated H2SO4. Can. J. Chem., 60: 2668-2674.

Brown, D.J., 2009. The Chemistry of Heterocyclic Compounds, The Pyrimidines. 1st Edn., John Wiley and Sons, New York, USA., ISBN-13: 9780470188255, Pages: 774.

Brown, D.J., R.F. Evans, W.B. Cowden and M.D. Fenn, 1994. The Pyrimidine. John Wiley and Sons, New York, USA., pp: 96-106.

Ceccherini, E., P. Indovina, C. Zamperini, E. Dreassi and N. Casini et al., 2015. SRC family kinase inhibition through a new pyrazolo[3,4-d]pyrimidine derivative as a feasible approach for glioblastoma treatment. J. Cell. Biochem., 116: 856-863.

Chang, J., J. Du and Y. Zheng, 2007. Synthesis and characterization of novel biodegradable polymeric prodrugs containing 5-fluorouracil and 4-amino-N-(2-pyrimidinyl) benzene sulfonamide terminal groups. J. Applied Polym. Sci., 105: 2339-2345.

Cheng, X.M., S.H. Wang, D.L. Cui and B. Li, 2015. The synthesis and herbicidal activity of 5-(substituted-phenyl)-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines. J. Heterocycl. Chem., 52: 607-610.

Cruickshank, K.A., J. Jiricny and C.B. Reese, 1984. The benzylation of uracil and thymine. Tetrahedron Lett., 25: 681-684.

Curphrey, T.J. and K.S. Prasad, 1972. Diquaternary salts. I. Preparation and characterization of the diquaternary salts of some diazines and diazoles. J. Org. Chem., 37: 2259-2266.

Danesh, A., J. Behravan and M. Rameza, 2015. Antiviral activity evaluation of some pyrimidine derivatives using plaque reduction assay. J. Chem. Pharm. Res., 7: 289-293.

Deng, Y.H., D. Xu, Y.X. Su, Y.J. Cheng and Y.L. Yang et al., 2015. Synthesis and biological evaluation of novel oxazolo[5,4-d]pyrimidines as potent VEGFR-2 inhibitors. Chem. Biodivers., 12: 528-537.

Diaz-Sanchez, B.R., M.A. Iglesias-Arteaga, R. Melgar-Fernandez and E. Juaristi, 2007. Synthesis of 2-substituted-5-halo-2,3-dihydro-4(H)-pyrimidin-4-ones and their derivatization utilizing the sonogashira coupling reaction in the enantioselective synthesis of α-substituted β-amino acids. J. Org. Chem., 72: 4822-4825.
Dondoni, A., A. Massi and S. Sabbatini, 2001. Towards the synthesis of C-glycosylated dihydropyrimidine libraries via the three-component Biginelli reaction. A novel approach to artificial nucleosides. Tetrahedron Lett., 42: 4495-4497.

Dondoni, A., A. Massi and S. Sabbatini, 2002. Improved synthesis and preparative scale resolution of racemic monastrol. Tetrahedron Lett., 43: 5913-5916.

El-Sayed, M. and S. Spange, 2007. Synthesis, properties and solvatochromism of 1,3-dimethyl-5-[(thien-2-yl)-[4-(1-piperidyl) phenyl]methylidene)-(1H,3H)-pyrimidine-2,4,6-trione. J. Phys. Org. Chem., 20: 264-270.

Fang, Z., D. Kang, L. Zhang, B. Huang and H. Liu et al., 2015. Synthesis and biological evaluation of a series of 2-((1-substituted-1H-1,2,3-triazol-4-yl)methylthio)-6-(naphthalen-1-ylmethyl)pyrimidin-4(3H)-one as potential HIV-1 inhibitors. Chem. Biol. Drug Des. 10.1111/cbdd.12524

Farlex Inc., 2015. The free dictionary. http://www.thefreedictionary.com/Pyrimidine.

Faty, R.M., M.S. Rashed and M.M. Youssef, 2015. Microwave-assisted synthesis and antimicrobial evaluation of novel spiroisoquinoline and spiropyrido[4,3-d]pyrimidine derivatives. Molecules, 20: 1842-1859.

Fernandez-Cureses, G., S. de Castro, M.L. Jimeno, J. Balzarini and M.J. Camarasa, 2015. Design, synthesis and biological evaluation of unconventional aminopyrimidine, aminopurine and amino-1,3,5-triazine methyloxynucleosides. ChemMedChem, 10: 321-335.

Ghebremariat, Y.T., D.A. Erlanson and J.P. Cooke, 2014. A novel and potent inhibitor of dimethylarginine dimethylaminohydrolase: A modulator of cardiovascular nitric oxide. J. Pharmacol. Exp. Therapeut., 348: 69-76.

Giordanetto, F., B. Barlaam, S. Berglund, K. Edman and O. Karlsson et al., 2014. Discovery of 9-(1-phenoxethyl)-2-morpholino-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxamides as oral PI3Kβ inhibitors, useful as antiplatelet agents. Bioorg. Med. Chem. Lett., 24: 3936-3943.

Gulcan, M., S. Ozdemir, A. Dundar, E. Ispir and M. Kurtoglu, 2014. Mononuclear complexes based on pyrimidine ring azo schiff-base ligand: Synthesis, characterization, antioxidant, antibacterial and thermal investigations. Zeitschrift Anorganische Allgemeine Chemie, 640: 1754-1762.

Gupta, J.K., A. Chaudhary, R. Dudhe, K. Varuna, P.K. Sharma and P.K. Verma, 2010. A review on the synthesis and therapeutic potential of pyrimidine derivatives. Int. J. Pharma. Sci. Res., 1: 34-49.

Gutierrez-Valero, M.D., M.L. Godino-Salido, P. Arranz-Mascaros, R. Lopez-Garzon, R. Cuesta and J. Garcia-Martin, 2007. Adsorption of designed pyrimidine derivative ligands on an activated carbon for the removal of Cu(II) ions from aqueous solution. Langmuir, 23: 5995-6003.

Hilmy, K.M.H., M.M.A. Khalifa, M.A.A. Hawata, R.M.A.A. Keshk and A.A. El-Torgman, 2010. Synthesis of new pyrrolo[2,3-d]pyrimidine derivatives as antibacterial and antifungal agents. Eur. J. Med. Chem., 45: 5243-5250.

Jain, K.S., T.S. Chitre, P.B. Miniyar, M.K. Kathiravan and V.S. Bendre et al., 2006. Biological and medicinal significance of pyrimidines. Curr. Sci., 90: 793-803.

Jang, M.Y., S. de Jonghe, K. Segers, J. Anne and P. Herdevijn, 2011. Synthesis of novel 5-amino-thiazolo[4,5-d]pyrimidines as E. Coli and S. Aureus SecA inhibitors. Bioorg. Med. Chem. Chem., 19: 702-714.

Kakiya, H., K. Yagi, H. Shinokubo and K. Oshima, 2002. Reaction of a,a-dibromo oxime ethers with grignard reagents: Alkylative annulation providing a pyrimidine core. J. Am. Chem. Soc., 124: 9032-9033.
Kappe, T., 1994. Nucleophilic and electrophilic substitutions at the pyridazine nucleus. Acta Chim. Slovenica, 41: 219-234.

Karpov, A.S. and T.J.J. Muller, 2003. Straightforward novel one-pot enaminone and pyrimidine syntheses by coupling-addition-cyclocondensation sequences. Synthesis, 18: 2815-2826.

Katritzky, A.R., J.W. Rogers, R.M. Witek and S.K. Nair, 2004. Novel syntheses of pyrido[1,2-a]pyrimidin-2-ones, 2H-quinolizin-2-ones, pyrido[1,2-a]quinolin-3-ones and thiazolo [3,2-a] pyrimidin-7-ones. Arkivoc, 8: 52-60.

Katzung, G.B., 1995. Basic and Clinical Pharmacology. 6th Edn., Appleton and Lange Publishing, Norwalk, CT., Pages: 671.

Kim, J.M., S.H. Kim and J.N. Kim, 2007. Synthesis of 2,4,6-trisubstituted pyrimidines from Baylis Hillman adducts and amidines. Bull. Korean Chem. Soc., 28: 2505-2507.

Lagoja, I.M., 2005. Pyrimidine as constituent of natural biologically active compounds. Chem. Biodivers., 2: 1-50.

Lawrence, H.R., K. Mahajan, Y. Luo, D. Zhang and N. Tindall et al., 2015. Development of novel ACK1/TNK2 inhibitors using a fragment-based approach. J. Med. Chem., 58: 2746-2763.

Lejeune, M., J.M. Rybicka and K. Chadee, 2009. Recent discoveries in the pathogenesis and immune response toward Entamoeba histolytica. Future Microbiol., 4: 105-118.

Liu, X.P., R.K. Narla and F.M. Uckun, 2003. Organic phenyl arsonic acid compounds with potent antileukemic activity. Bioorg. Med. Chem. Lett., 13: 581-583.

Liu, Z., Y. Wang, H. Lin, D. Zuo, L. Wang, Y. Zhao and P. Gong, 2014a. Design, synthesis and biological evaluation of novel thieno[3,2-d]pyrimidine derivatives containing diaryl urea moiety as potent antitumor agents. Eur. J. Med. Chem., 85: 215-227.

Liu, Z.Y., T. Wenzler, R. Brun, X. Zhu and D.W. Boykin, 2014b. Synthesis and antiparasitic activity of new bis-arylimidamides: DB766 analogs modified in the terminal groups. Eur. J. Med. Chem., 83: 167-173.

Ma, H.J., J.H. Zhang, X.D. Xia, J. Kang and J.H. Li, 2014a. Design, synthesis and herbicidal evaluation of novel 4-(1H-pyrazol-1-yl)pyrimidine derivatives. Pest Manag. Sci. 10.1002/ps.3918

Ma, H.J., J.H. Zhang, X.D. Xia, M.H. Xu, J. Ning and J.H. Li, 2014b. Design, synthesis and herbicidal activities of novel 4-(1H-pyrazol-1-yl)-6-(alkynlyloxy)-pyrimidine derivatives as potential pigment biosynthesis inhibitors. Pest Manag. Sci., 70: 946-952.

Ma, L.Y., Y.C. Zheng, S.Q. Wang, B. Wang and Z.R. Wang et al., 2015. Design, synthesis and structure-activity relationship of novel LSD1 inhibitors based on pyrimidine-thiourea hybrids as potent, orally active antitumor agents. J. Med. Chem., 58; 1705-1716.

Maddila, S., S. Gorle, N. Seshadri, P. Lavanya and S.B. Jonnalagadda, 2013. Synthesis, antibacterial and antifungal activity of novel benzothiazole pyrimidine derivatives. Arabian J. Chem. 10.1016/j.arabjc.2013.04.003

Malnut, V., L.P. Slavetinska, P. Naus, P. Dzubak and M. Hajduch et al., 2015. 2-Substituted 6-(het)aryl-7-deazapurine ribonucleosides: Synthesis, inhibition of adenosine kinases and antimycobacterial activity. ChemMedChem, 10: 1079-1093.

Manohar, S., U.C. Rajesh, S.I. Khan, B.L. Tekwani and D.S. Rawat, 2012. Novel 4 aminoquinoline-pyrimidine hybrids with improved in vitro and in vivo antimalarial activity. ACS Med. Chem. Lett., 3: 555-559.

Mathews, A. and C.V. Asokan, 2007. Synthesis of pyrimidine-5-carbaldehydes from α-formylaroyketene dithioacetals. Tetrahedron, 63: 7845-7849.
Mavrova, A.T., D. Wesselinova, J.A. Tsenov and L.A. Lubenov, 2014. Synthesis and antiproliferative activity of some new thieno [2,3-d] pyrimidin-4(3H)-ones containing 1,2,4-triazole and 1,3,4-thiadiazole moiety. Eur. J. Med. Chem., 86: 676-683.

Meng, G., Y. Liu, A. Zheng, F. Chen and W. Chen et al., 2014. Design and synthesis of a new series of modified CH-diarylpyrimidines as drug-resistant HIV non-nucleoside reverse transcriptase inhibitors. Eur. J. Med. Chem., 82: 600-611.

Menor-Salvan, C., D.M. Ruiz-Bermejo, M.I. Guzman, S. Osuna-Esteban and S. Veintemillas-Verdaguer, 2009. Synthesis of pyrimidines and triazines in ice: Implications for the prebiotic chemistry of nucleobases. Chem. Eur. J., 15: 4411-4418.

Mobinikhaledi, A., N. Forughifar, J.A. Safari and E. Amini, 2007. Synthesis of some 2-oxo and 2-thioxo substituted pyrimidines using solvent-free conditions. J. Heterocycl. Chem., 44: 697-699.

Mohamed, A.M., H.R.M. Al-Qalawi, W.E. El-Sayed, W.A.A. Arafa, M.S. Alhumaimess and A.K. Hassan, 2015a. Anticancer activity of newly synthesized triazolopyrimidine derivatives and their nucleoside analogs. Acta Poloniae Pharm. Drug Res., 72: 307-318.

Mohamed, M.S., R.H. Abd El-Hameed, A.I. Sayed and S.H. Soror, 2015b. Novel antiviral compounds against gastroenteric viral infections. Arch. Pharm. Chem. Life Sci., 348: 194-205.

Moustafa, A.H., H.A. Saad, W.S. Shehab and M.M. El-Mobayed, 2007. Synthesis of some new pyrimidine derivatives of expected antimicrobial activity. Phosphorus Sulfur Silicon Relat. Elem., 183: 115-135.

Movassaghi, M. and M.D. Hill, 2006. Single-step synthesis of pyrimidine derivatives. J. Am. Chem. Soc., 128: 14254-14255.

Nagaraj, A. and C.S. Reddy, 2007. Synthesis and biological study of novel bis-chalcones, bis-thiazines and bis-pyrimidines. J. Iran. Chem. Soc., 5: 262-267.

Nandre, J., S. Patil, V. Patil, F. Yu and L. Chen et al., 2014. A novel fluorescent turn-on chemosensor for nanomolar detection of Fe(III) from aqueous solution and its application in living cells imaging. Biosens. Bioelectron., 61: 612-617.

Nguyen, S.T., J.D. Williams, M.M. Butler, X. Ding and D.M. Mills et al., 2014. Synthesis and antibacterial evaluation of new, unsymmetrical triaryl bisamidine compounds. Bioorg. Med. Chem. Lett., 24: 3366-3372.

Okazaki, S., S. Oishi, T. Mizuhara, K. Shimura and H. Murayama et al., 2015a. Investigations of possible prodrug structures for 2-(2-mercaptophenyl)tetrahydropyrimidines: Reductive conversion from anti-HIV agents with pyrimidobenzothiazine and isothiazolopyrimidine scaffolds. Org. Biomol. Chem., 13: 4706-4713.

Okazaki, S., T. Mizuhara, K. Shimura, H. Murayama and H. Ohno et al., 2015b. Identification of anti-HIV agents with a novel benzo[4,5]isothiazolo[2,3-a]pyrimidine scaffold. Bioorg. Med. Chem., 23: 1447-1452.

Okuda, K., T. Hirota and K. Sasaki, 2014a. Polycyclic N-heterocyclic compounds. Part 82: Synthesis and evaluation of anti-platelet aggregation activity of 2,4-disubstituted 5,6-dihydro[1]benzothiepin[5,4-d]pyrimidine and related compounds. J. Heterocycl. Chem., 51: 911-920.

Okuda, K., Y. Yamamoto, T. Hirota and K. Sasaki, 2014b. Polycyclic N-heterocyclic compounds. Part 75: Synthesis of 2,4-disubstituted 5,6-dihydro[1]benzo[xepino][5,4-d]pyrimidines and 12-substituted 1,2,4,5-tetrahydro[1]benzoepinox[4,5-e]imidazo[1,2-c]pyrimidines as potential antiplatelet aggregators. J. Heterocycl. Chem., 51: 972-981.
Panda, S.S. and P.V.R. Chowdary, 2008. Synthesis of novel indolyl-pyrimidine antiinflammatory, antioxidant and antibacterial agents. Indian J. Pharm. Sci., 70: 208-215.

Paronikyan, E.G., A.S. Noravanyan, S.F. Akopyan, I.A. Dzhagatspanyan, I.M. Nazaryan and R.G. Paronikyan, 2007. Synthesis and anticonvulsant activity of pyrano[4,3 :4,5]pyrido[2,3-b]thieno[3,2-d] pyrimidine derivatives and pyrimido[5,4 :2,3]-thieno[2,3-c]isoquinoline derivatives. Pharm. Chem. J., 41: 466-469.

Parveen, H., F. Hayat, A. Salahuddin and A. Azam, 2010. Synthesis, characterization and biological evaluation of novel 6-ferrocenyl-4-aryl-2-substituted pyrimidine derivatives. Eur. J. Med. Chem., 45: 3497-3503.

Pogorelecnik, B., M. Brvar, B. Zegura, M. Filipic, T. Solmajer and A. Perdih, 2015. Discovery of mono- and disubstituted 1H-Pyrazolo[3,4]pyrimidines and 9H-purines as catalytic inhibitors of human DNA Topoisomerase IIα. ChemMedChem, 10: 345-359.

Prajapati, D., K.J. Borah and M. Gohain, 2007. An efficient regiospecific synthesis of highly functionalized novel dihydropyrimido[4,5-d]pyrimidine derivatives by a three-component one-pot-condensation under solvent-free conditions. Synlett, 4: 595-598.

Raj, K.K.V., B. Narayana, B.V. Ashalatha and N.S. Kumari, 2006. New thiazoles containing pyrazolopyrimidine moiety as possible analgesic agents. J. Pharmacol. Toxicol., 1: 559-565.

Rao, N.V., N. Vaisalini, B. Mounika, V. Harika, P.K. Desu and S. Nama, 2013. An overview on synthesis and biological activity of pyrimidines. Int. J. Pharm. Chem. Res., 2: 14-22.

Rashid, M., A. Husain, M. Shaharyar, R. Mishra, A. Hussain and O. Afzal, 2014. Design and synthesis of pyrimidine molecules endowed with thiazolidin-4-one as new anticancer agents. Eur. J. Med. Chem., 83: 630-645.

Rathore, A., M.U. Rahman, A.A. Siddiqui, A. Ali and M. Shaharyar, 2014. Design and synthesis of benzimidazole analogs endowed with oxadiazole as selective COX-2 inhibitor. Arch. Pharm. Chem. Life Sci., 347: 923-935.

Read, M.L., M. Braendvang, P.O. Miranda and L.L. Gundersen, 2010. Synthesis and biological evaluation of pyrimidine analogs of antimycobacterial purines. Bioorg. Med. Chem., 18: 3885-3897.

Rindhe, S.S., P.N. Mandhare, L.R. Patil and R.A. Mane, 2005. Synthesis and antifungal activity of 2-amino-6-substituted thiazolyl-pyrimidines. Indian J. Heterocyclic Chem., 15: 133-136.

Ruiz-Mirazo, K., C. Briones and A. de la Escosura, 2014. Prebiotic systems chemistry: New perspectives for the origins of life. Chem. Rev., 114: 285-366.

Saif, M.W., 2005. An adverse interaction between warfarin and fluoropyrimidines revisited. Clin. Colorectal Cancer, 5: 175-180.

Saikia, P., P.P. Kaishap, R. Prakash, K. Shekarrao, S. Gogoi and R.C. Boruah, 2014. A facile one-pot synthesis of 7-substituted pyrazolo[1,5-a]pyrimidines by base induced three-component reaction. Tetrahedron Lett., 55: 3896-3900.

Sayed, H.H., A.H. Shamroukh and A.E. Rashad, 2006. Synthesis and biological evaluation of some pyrimidine, pyrimido[2,1-b][1,3]thiazine and thiazolo[3,2-a]pyrimidine derivatives. Acta Pharm., 56: 231-244.

Selvam, T.P., C.R. James, P.V. Dniandev and S.K. Valzita, 2012. A mini review of pyrimidine and fused pyrimidine marketed drugs. Res. Pharm., 2: 1-9.

Shakya, N., N.C. Srivastav, S. Bhavanam, C. Tse and N. Desroches et al., 2012. Discovery of novel 5-(ethyl or hydroxymethyl) analogs of 2′-‘up’ fluoro (or hydroxyl) pyrimidine nucleosides as a new class of Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium inhibitors. Bioorg. Med. Chem., 20: 4088-4097.
Sharma, M., V. Deekshith, A. Semwal, D. Sriram and P. Yogeeswari, 2014. Discovery of tetrahydropyrido[4,3-d]pyrimidine derivatives for the treatment of neuropathic pain. Bioorg. Chem., 52: 69-76.

Singh, K., H. Kaur, P. Smith, C. de Kock, K. Chibale and J. Balzarini, 2014. Quinoline-pyrimidine hybrids: Synthesis, antiplasmodial activity, SAR and mode of action studies. J. Med. Chem., 57: 435-448.

Soliman, A.M., S.K. Mohamed, M. Abd El Aleem, A.A. El-Remaily and H. Abdel-Ghany, 2014. Synthesis of pyrimidine, dihydropyrimidinone and dihydroimidazole derivatives under free solvent conditions and their antibacterial evaluation. J. Heterocycl. Chem., 51: 1202-1209.

Thore, S.N., S.V. Gupta and K.G. Baheti, 2015. Synthesis and pharmacological evaluation of novel triazolo[4,3-a]tetrahydrobenzo(b)thieno[3,2-e]pyrimidine-5(4H)-ones. J. Heterocycl. Chem., 52: 142-149.

Tian, Y., D. Du, D. Rai, L. Wang and H. Liu et al., 2014. Fused heterocyclic compounds bearing bridgehead nitrogen as potent HIV-1 NNRTIs. Part 1: Design, synthesis and biological evaluation of novel 5,7-disubstituted pyrazolo[1,5-a]pyrimidine derivatives. Bioorg. Med. Chem., 22: 2052-2059.

Trivedi, A.R., A.B. Siddiqui and V.H. Shah, 2008. Design, synthesis, characterization and antitubercular activity of some 2-heterocycle-substituted phenothiazines. Arkivoc, 2: 210-217.

Udupi, R.H., T.Y. Pasha and A.R. Bhat, 2005. Synthesis and antimicrobial screening of some pyrimidine derivatives. Indian J. Heterocycl. Chem., 15: 149-152.

Undheim, K. and T. Benneche, 1996. Pyrimidines and their Benzo Derivatives. In: Comprehensive Heterocyclic Chemistry II, Boulton, A.J. (Ed.), Vol. 6, Elsevier Science Ltd., Oxford, UK., pp 96-231.

Verma, A., L. Sahu, N. Chaudhary, T. Dutta, D. Dewangan and D.K. Tripathi, 2012. A review: Pyrimidine their chemistry and pharmacological potentials. Asian J. Biochem. Pharm. Res., 2: 2231-2560.

Wade, Jr. L.G., 1999. Organic Chemistry. 4th Edn., Prentice-Hall, New York, USA., pp: 709-715.

Wang, L., Y. Tian, W. Chen, H. Liu and P. Zhan et al., 2014. Fused heterocycles bearing bridgehead nitrogen as potent HIV-1 NNRTIs. Part 2: Discovery of novel [1,2,4]Triazolo[1,5-a]pyrimidines using a structure-guided core-refining approach. Eur. J. Med. Chem., 85: 293-303.

Wang, Y., S. Mitchell-Ryan, S. Raghavan, C. George and S. Orr et al., 2015. Novel 5-substituted pyrrolo[2,3-d]pyrimidines as dual inhibitors of glycinamide ribonucleotide formyltransferase and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase and as potential antitumor agents. J. Med. Chem., 58: 1479-1493.

Woodgate, P.D., J.M. Herbert and W.A. Denny, 1987. The preparation of pyrido[4,3,2-de]quinazoline and pyrido[3,4,5-de]quinazoline. Heterocycles, 26: 1029-1036.

Wu, W.N., A.Q. Tai, Q. Chen and G.P. Ouyang, 2015. Synthesis and antiviral bioactivity of novel 2-substituted methylthio-5-(4-amino-2-methylpyrimidin-5-yl)-1,3,4-thiadiazole derivatives. J. Heterocycl. Chem. 10.1002/jhet.2435

Yadava, U., B.K. Shukla, M. Roychoudhury and D. Kumar, 2015. Pyrazolo[3,4-d]pyrimidines as novel inhibitors of O-acetyl-1-serine sulfhydrylase of Entamoeba histolytica: An in silico study. J. Mol. Mod. 10.1007/s00894-015-2631-3

Zhao, B., Y. Xu, Q.G. Deng, Z. Liu, L.Y. Wang and Y. Gao, 2014. One-pot, three component synthesis of novel 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives by microwave irradiation. Tetrahedron Lett., 55: 4521-4524.