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

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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

(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 B_1) (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 $C_4H_4N_2$ 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 (1.35-1.40Å), 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 pK_a 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 pK_a values of pyrimidine derivatives had also been documented in both basic and acidic media. The basic pK_a 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 pK_a values were 9.2, 8.6 and 6.8, respectively. An extensive compilation and tabulation of acidic and basic pK_a 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).

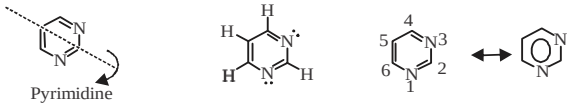


Fig. 1: Structure of un-substituted pyrimidine showing its one plane of symmetry

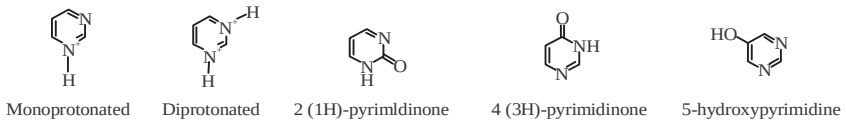


Fig. 2: Structural attribute showing pKa of protonated and non-protonated pyrimidines

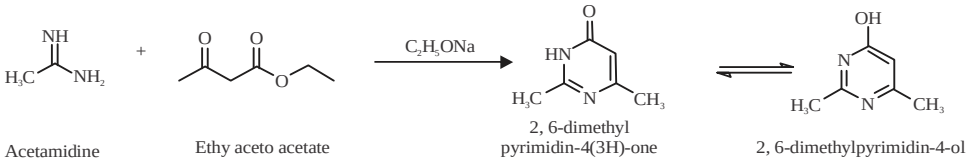


Fig. 3: Cycloadditive synthesis of 4-hydroxy-2,6-dimethylpyrimidine

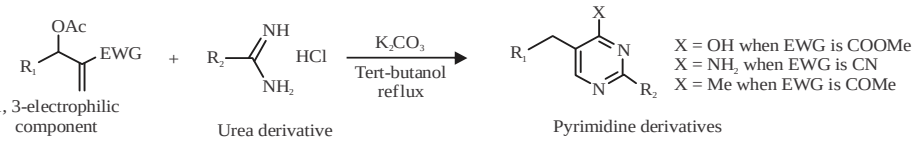


Fig. 4: Synthesis of 2,4,5-trisubstituted pyrimidine via 1,3-dielectrophilic strategy

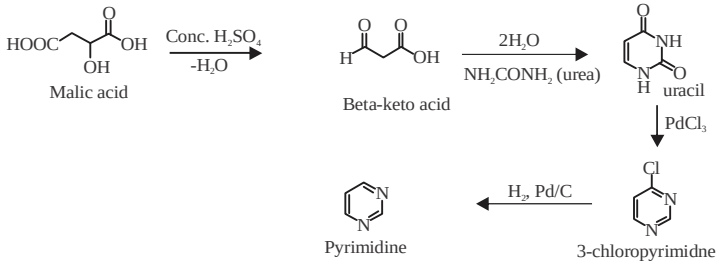


Fig. 5: Intramolecular cyclization to afford non-substituted pyrimidine

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_2CO_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 produces uracil which was easily converted to pyrimidine via chlorination and hydrogenation processes. This involves an initial decarboxylation of malic acid under the influence of concentrated H_2SO_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).

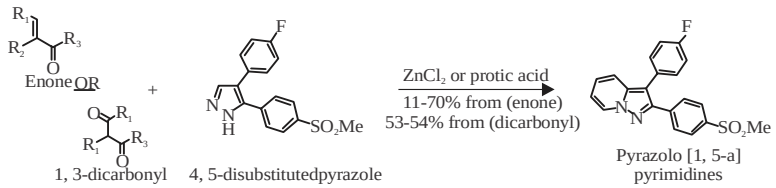


Fig. 6: Synthesis of pyrazolo[1,5-a] pyrimidines from amidine

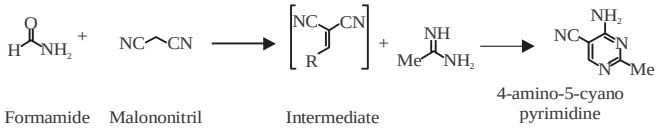


Fig. 7: Synthesis of 4-amino-5-cyano-2-methyl pyrimidine

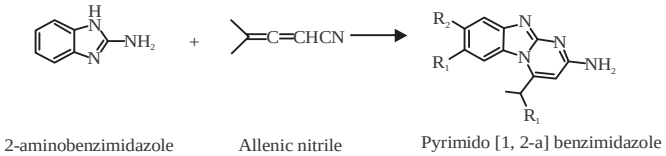


Fig. 8: Synthesis of pyrimido[1,2-a] benzimidazole from allenic nitrile

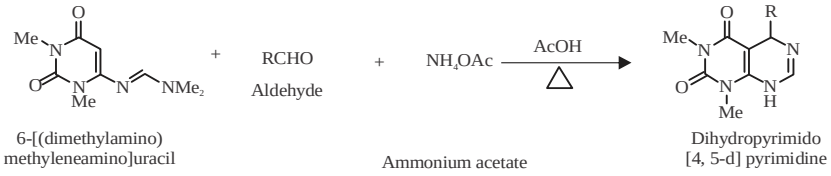


Fig. 9: Solvent-free green approach to dihydropyrimido[4,5-d] pyrimidine

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)methylene amino] uracil, an aldehyde and NH_4OAc 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 $POCl_3$ 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(1*H*)-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

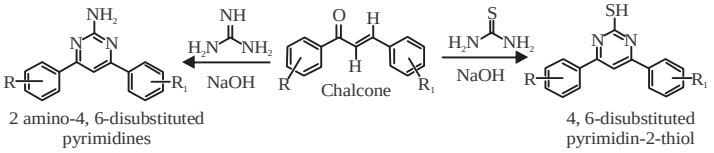


Fig. 10: Preparation of 4,6-diphenylpyrimidine from chalcone

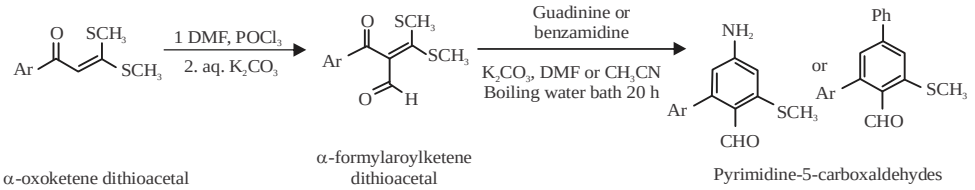


Fig. 11: Preparation of pyrimidine-5-carboxaldehydes from dithioacetal

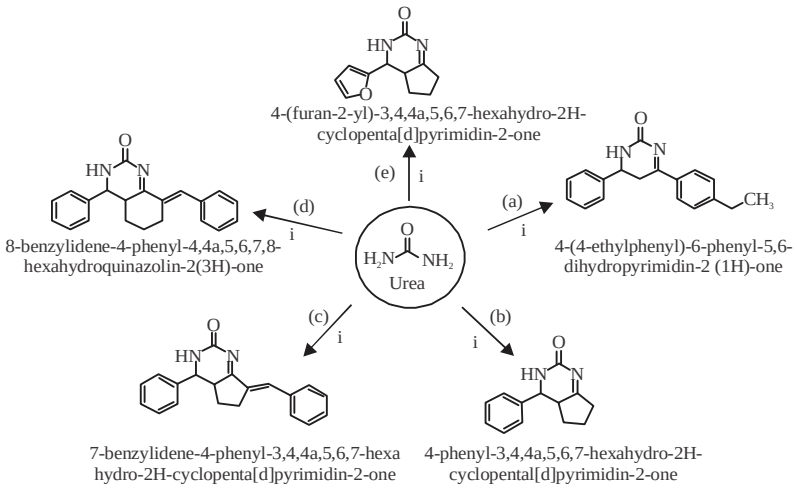


Fig. 12: SSA-assisted catalytic synthesis of pyrimidine derivatives

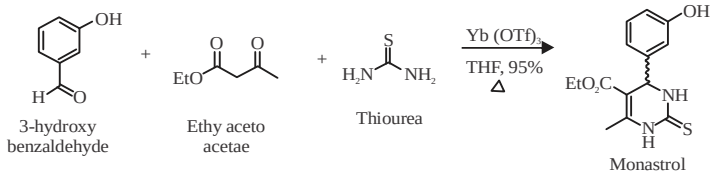


Fig. 13: Microwave-assisted synthesis of monastrol in excellent yield

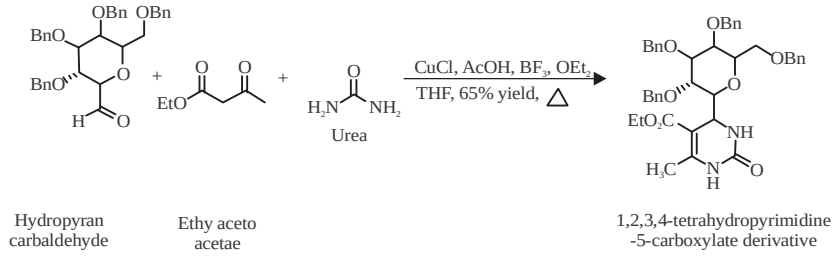


Fig. 14: Lewis acid synthesis of 1,2,3,4-tetrahydropyrimidine-5-carboxylate

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).

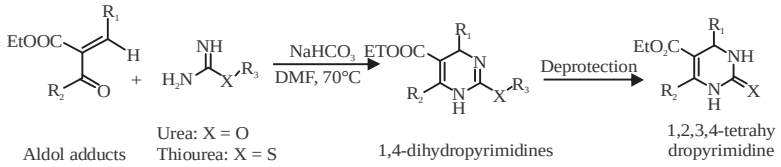


Fig. 15: 1,2,3,4-tetrahydropyrimidine from aldol-mediated Biginelli reaction

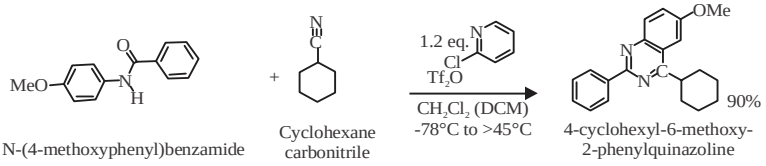


Fig. 16: Synthesis of benzofused-2-phenylpyrimidine from amide activation

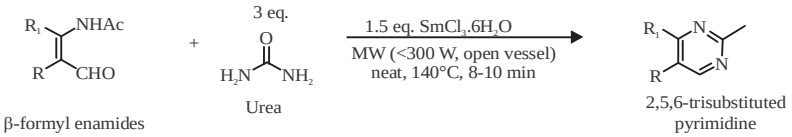


Fig. 17: 2,5,6-trisubstituted pyrimidine via $SmCl_3$-catalyzed cyclization

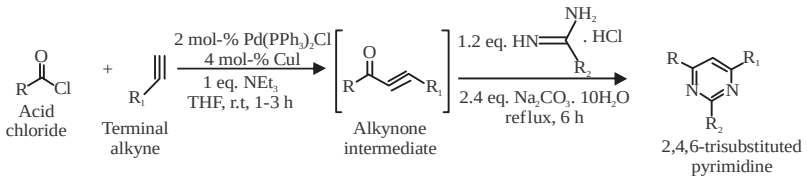


Fig. 18: 2,4,6-trisubstituted pyrimidine via cross coupling initiation

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 (Movassaghi 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 meterorite 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 5*H*-[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-5*H*-[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-α]pyrimidin-2-ones and 2*H*-quinolizin-2-ones, known

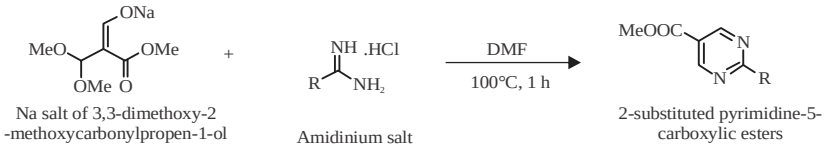


Fig. 19: Synthesis of 2-substitutedpyrimidine-5-carboxylic esters

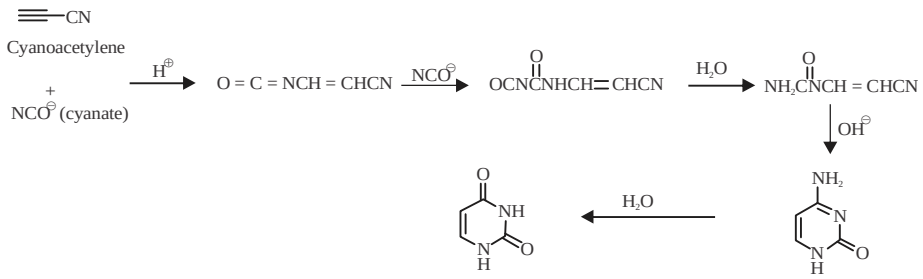


Fig. 20: Prebiotic synthesis of cytosine, a core pyrimidine in DNA

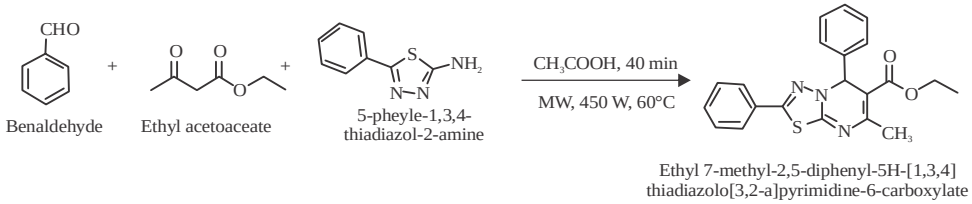


Fig. 21: Microwave-assisted synthesis of thiadiazolo-fused pyrimidine derivatives

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-a]pyrimidines is described by a one-pot reaction of steroidal/nonsteroidal ketones, aromatic aldehydes and 3-amino-1*H*-pyrazoles/5-amino-1*H*-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-2*H*-pyran-3-carbonitriles with 2-amino-benzothiazole 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).

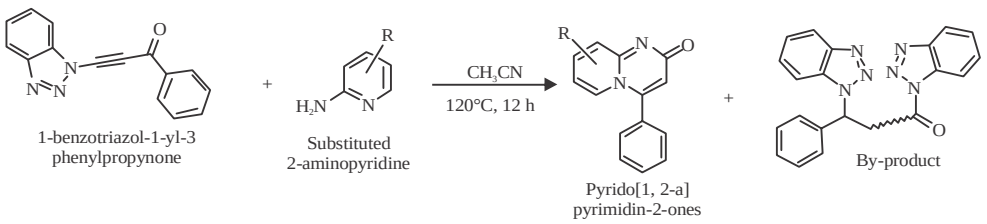


Fig. 22: Synthesis of pyrido[1,2-α] pyrimidin-2-ones from 2-propynone synthon

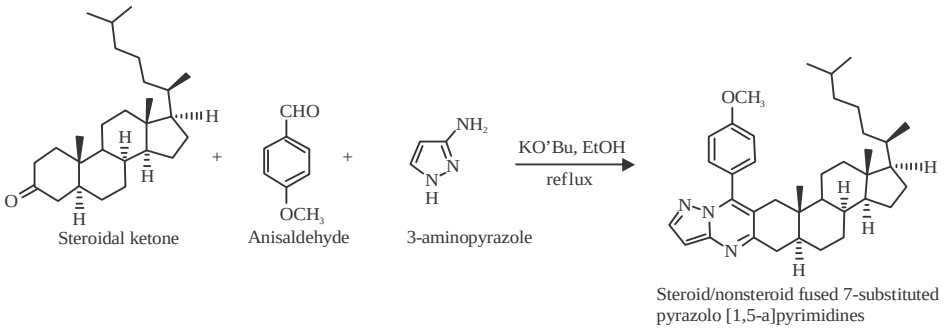


Fig. 23: Synthesis of steroid-fused 7-substituted pyrazolo[1,5-α]pyrimidines

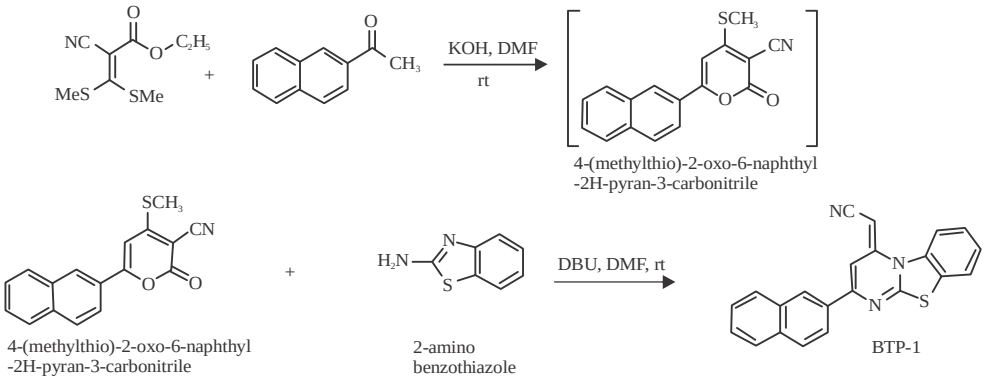


Fig. 24: Synthesis of tricyclic pyrimidine chemosensor, BTP-1

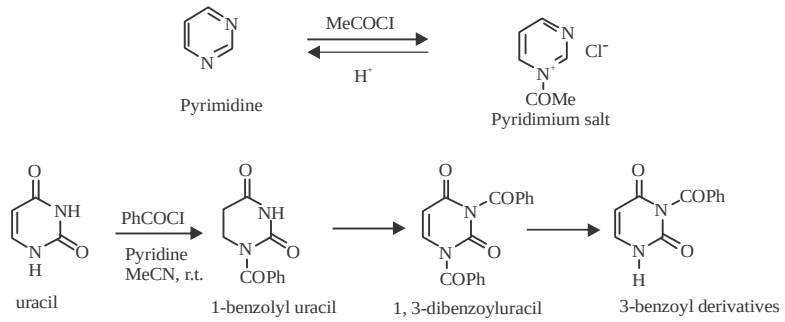


Fig. 25: Acylation reaction of pyrimidine derivatives at the nitrogen

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-methylpyrimidin 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).

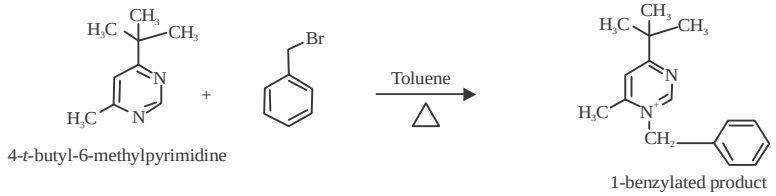


Fig. 26: Alkylation reaction of pyrimidine derivatives at the nitrogen

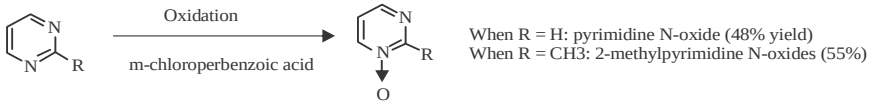


Fig. 27: Oxidation reaction of 2-substituted pyrimidine at the nitrogen

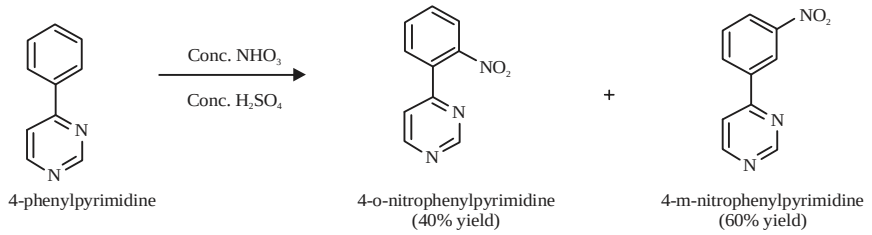


Fig. 28: Nitration reaction of pyrimidine derivatives at the carbon

Nitration at the carbon: Pyrimidine and its cation are highly π-deficient and resist nitration. The π-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).

Nitrosation at carbon: 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).

Alkoxylation and aryloxylation at carbon: Nucleophilic displacement of 2- and 4/6-halo substituents by alkoxyl or aryloxy ions occurred readily except in the presence of strongly electron-releasing substituents in the ring (Undheim and Benneche, 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

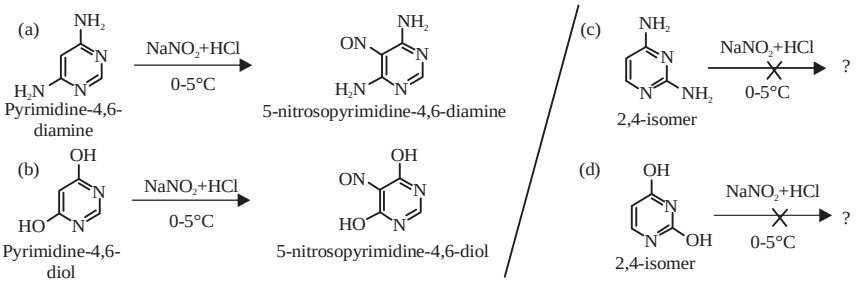


Fig. 29(a-d): Nitrosation reaction of pyrimidine derivatives at the carbon

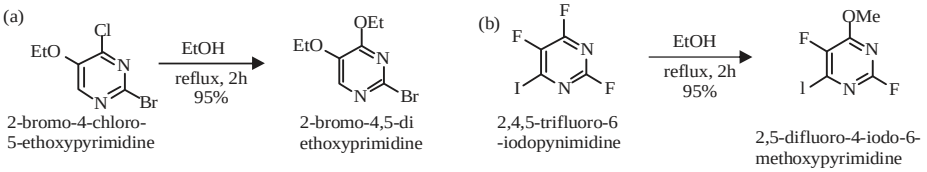


Fig. 30(a-b): Alkoxylation and aryloxylation reactions of pyrimidine derivatives at the carbon

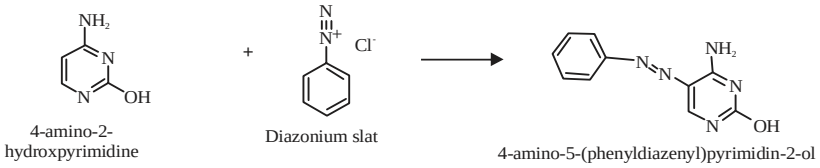


Fig. 31: Diazo coupling reaction of 4-amino-2-hydroxypyrimidine

2,4,5-trifluoro-6-iodopyrimidine, it was the fluorine in the 4-position which suffered preferential methanolysis to form the 2,5-difluoro-4-iodo-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.

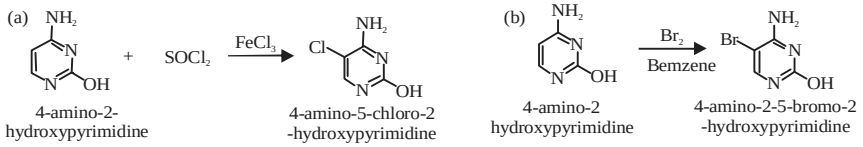


Fig. 32(a-b): Halogenation reaction of 4-amino-2-hydroxypyrimidine

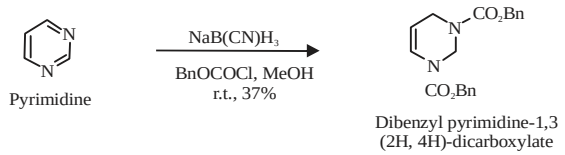


Fig. 33: Reduction reaction of un-substituted pyrimidine

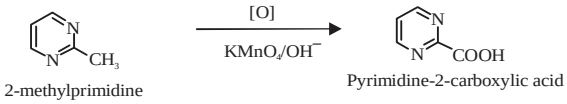


Fig. 34: Oxidation reaction of 2-substituted pyrimidine

Reduction of pyrimidine: The reduction of pyrimidine by $NaB(CN)H_3$ in methanol, with concurrent trapping of the reduced forms by benzyl chloroformate, was reported to give the dibenzyl pyrimidine-1,3(2*H*,4*H*)-dicarboxylate called the pyrimidine enamine (Undheim and Benneche, 1996) as shown in Fig. 33.

Oxidation of pyrimidine: The 2-methylgroup 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, Cp_2Mn, with an equimolar amount of the Li^+ salt of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-α]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 manganate cage compound $[LiMn(hpp)_3]_2$ via dimerization of a trisorganomanganate monomer. A series of biodegradable polymers containing

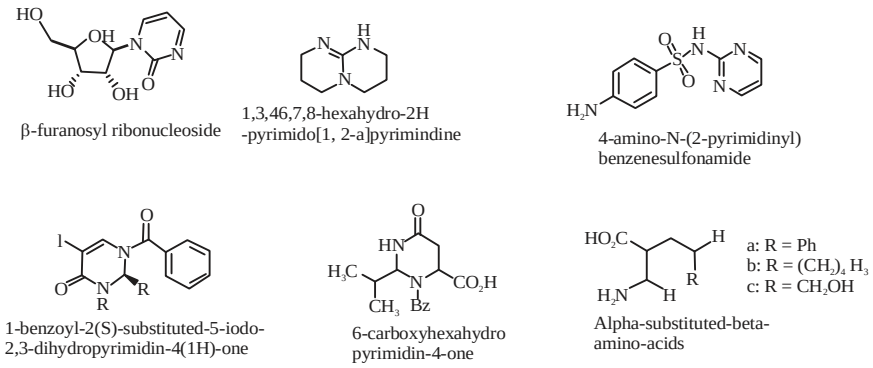


Fig. 35: Valuable products obtained from synthetic application of pyrimidine derivatives

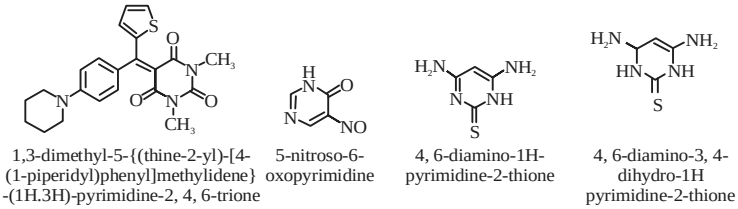


Fig. 36: Other reported synthetic modification of pyrimidine in new compounds design

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-dihydroxymethyl-5-fluorouracil (Chang *et al*., 2007). A one-pot synthesis of 1-benzoyl-2(S)-substituted-5-iodo-2,3-dihydro pyrimidin-4(1*H*)-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]methylidene}-(1*H*,3*H*)-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 Cu^{2+} 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 $BnNEt_3Cl$ as catalyst and under solvent-free conditions (Mobinikhaledi *et al*., 2007). Similarly, a successful protocol for the hydrogenation of 4,6-diamino-1*H*-pyrimidine-2-thione to 4,6-diamino-3,4-dihydro-1*H*-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(1*H*)-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

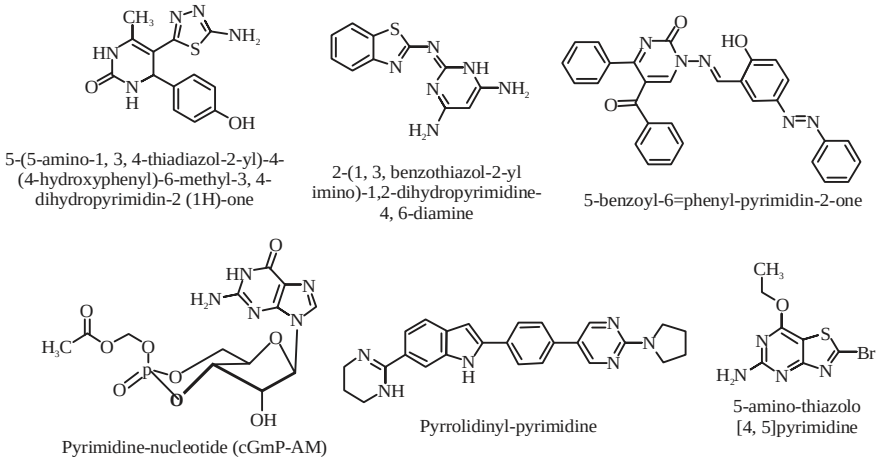


Fig. 37: Selected pyrimidine moieties with antibacterial activity

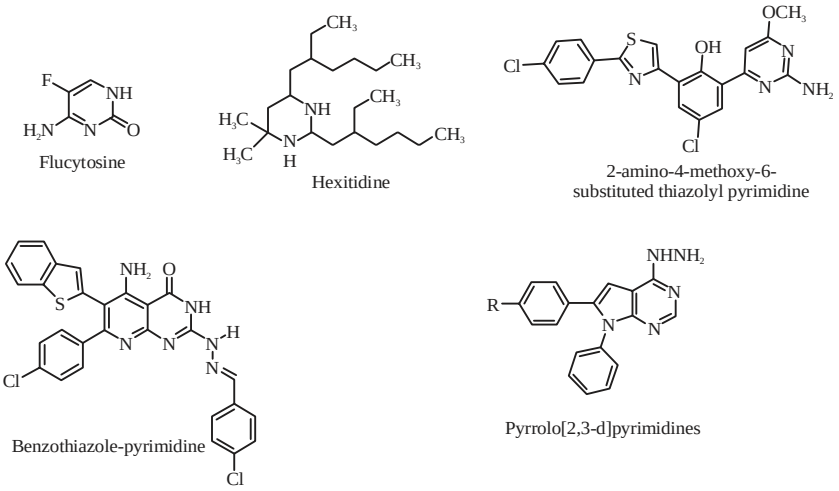


Fig. 38: Selected pyrimidine moieties with antifungal activity

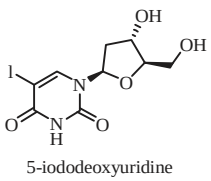
pyrimidines harvested in literatures as probable antibacterial agents include 5-benzoyl-6-phenylpyrimidin-2-one (Gulcan *et al*., 2014), pyrimidine-nucleotide (cGMP-AM) (Beckert *et al*., 2014), pyrrolidinyl-pyrimidine (Nguyen *et al*., 2014) and 5-amino-thiazolo[4,5-d]pyrimidine (Jang *et al*., 2011) 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).

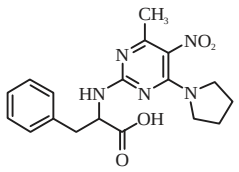
Antiviral activity: Recently, pyrimidine-based compounds and derivatives have a wide interest due to their useful antiviral properties. 5-iododeoxyuridine is pyrimidine-based heterocyclic antiviral agents that have been used extensively for the treatment of viral infections (Jain *et al*., 2006). 2-(4-methyl-5-nitro-6-(pyrrolidin-1-yl)-pyrimidin-2-ylamino)-3-phenylpropanoic 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-7*H*-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]pyrimidin-4(3*H*)-one was reported to show improved activity against lung and breast cancer (Mavrova *et al*., 2014) (Fig. 40).

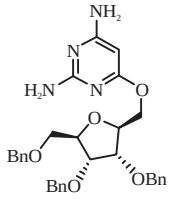
Antitubercular activity: Tuberculosis is an infectious disease that is caused by the bacterium *Mycobacterium tuberculosis*. Capreomycin and viomycin, shown in Fig. 41, are commercially available pyrimidine-containing antitubercular drugs (Jain *et al*., 2006). Deazapurine nucleoside (IC_{50} = 0.0012±0.0001 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),



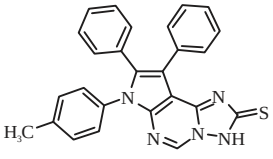
5-iododeoxyuridine



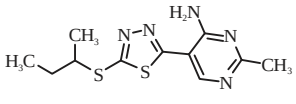
2-(4-methyl-5-nitro-6-(pyrrolidin-1-yl)-pyrimidin-2-ylamino)-3-phenylpropanoic acid



2,4-diaminopyrimidine derivative



7-(4-methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e] [1,2,4]-triazolo[1,5-c]pyrimidine-2-thione



5-(5-(Sec-butylthio)-1,3,4-thiadiazole -2-yl)-2-methylpyrimidin-4-amine

Fig. 39: Selected pyrimidine moieties with antiviral activity

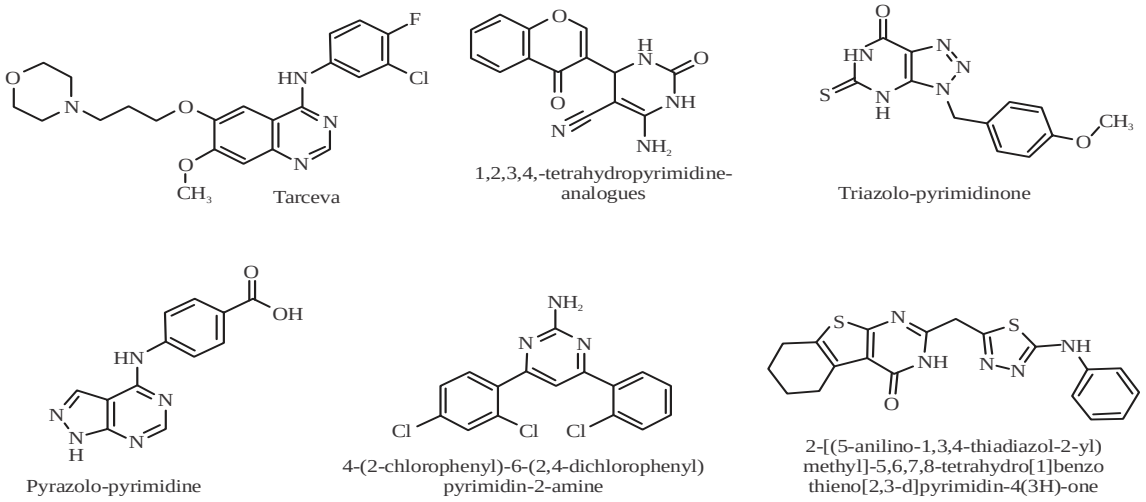


Fig. 40: Selected pyrimidine moieties with anticancer activity

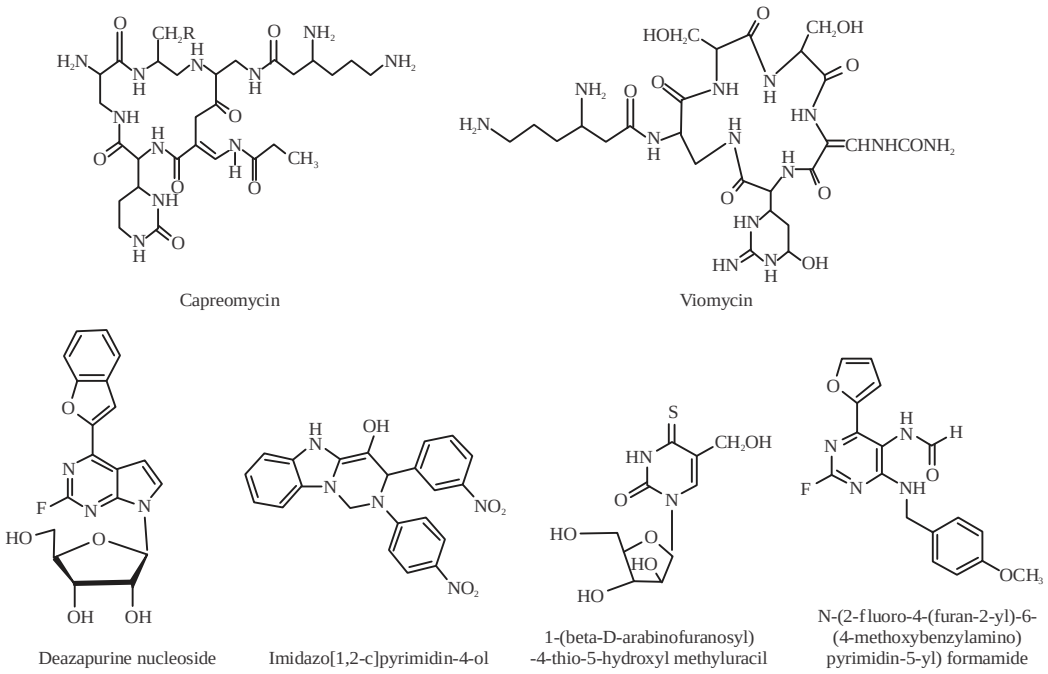


Fig. 41: Selected pyrimidine moieties with antitubercular activity

1-(β-D-arabinofuranosyl)-4-thio-5-hydroxylmethyluracil, showed in Fig. 41. was the most active with $MIC_{50} = 0.5\ \mu g\ mL^{-1}$. *N*-(2-fluoro-4-(furan-2-yl)-6-(4-methoxybenzyl amino)pyrimi din-5-yl)form amide inhibited the growth of *M. tb* $H_{37}Rv$ at IC_{90} <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-

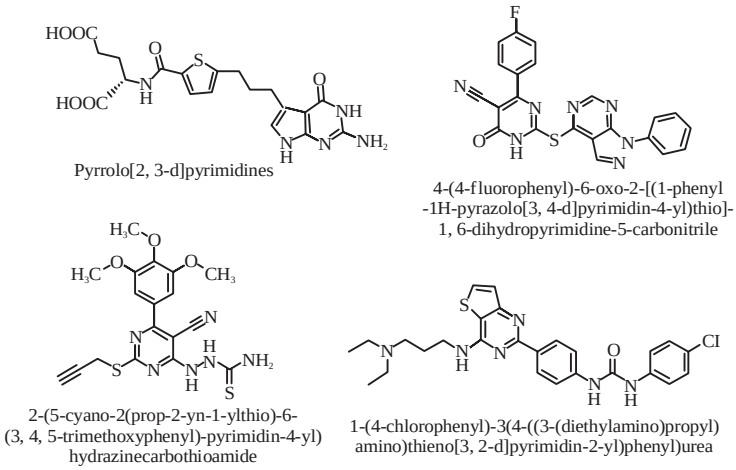


Fig. 42: Selected pyrimidine moieties with antitumor activity

henyl-1*H*-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-(4-((3-(diethylamino)propyl)amino) thieno[3,2-*d*]pyrimidin-2-yl)phenyl)urea showed antitumor activities with IC_{50} 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)-1*H*-benzo[*d*] imidazole showed in Fig. 43, was a selective COX-2 inhibitor with IC_{50} 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)-1*H*-benzo[*d*]imidazole has dual action as anticancer and anti-inflamm atory pyrimidine (Rathore *et al*., 2014). According to Sharma *et al.* (2014), *N*-(4-hydroxy -6-tosyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-yl)-4-nitrobenzamide (IC_{50} = 254 μM) and *N*-(4-hydroxy-6-tosyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-yl)isonicotin amide (IC_{50} = 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-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*) -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 IC_{50} 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, N^1-(7-chloroquinolin-4-yl)-N^3-(4-(piperidin-1-yl)pyrimidin-2-yl)propane-1,3-diamine screened by Singh *et al.* (2014) and N^1-(7-chloroquinolin-4-yl)-N^2-(6-methyl-

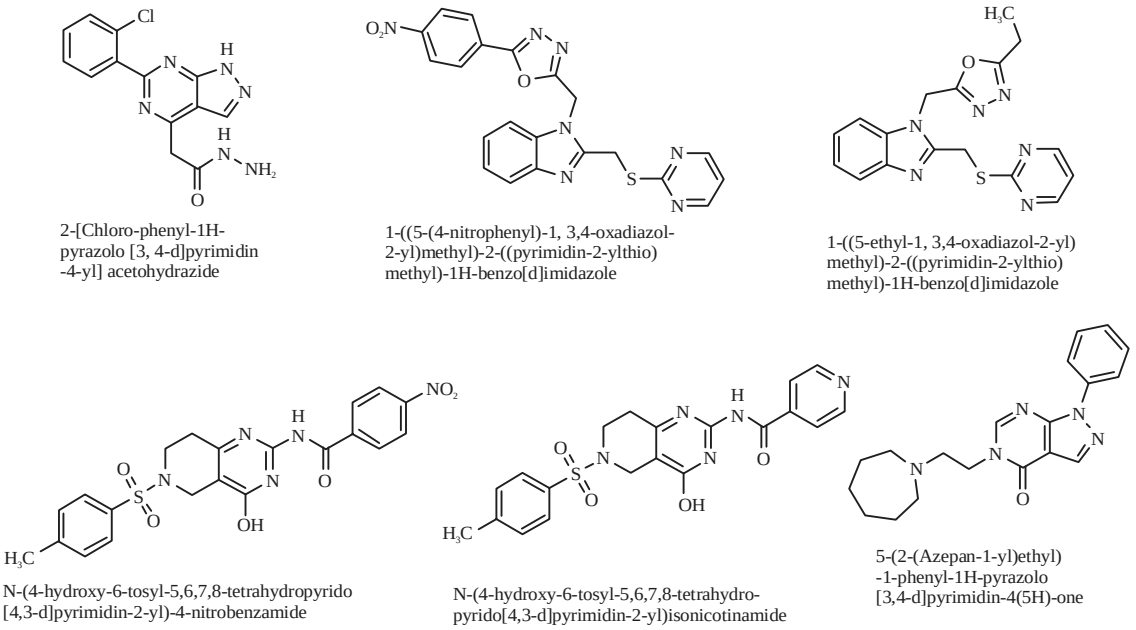


Fig. 43: Selected pyrimidine moieties with analgesic and anti-inflammatory activity

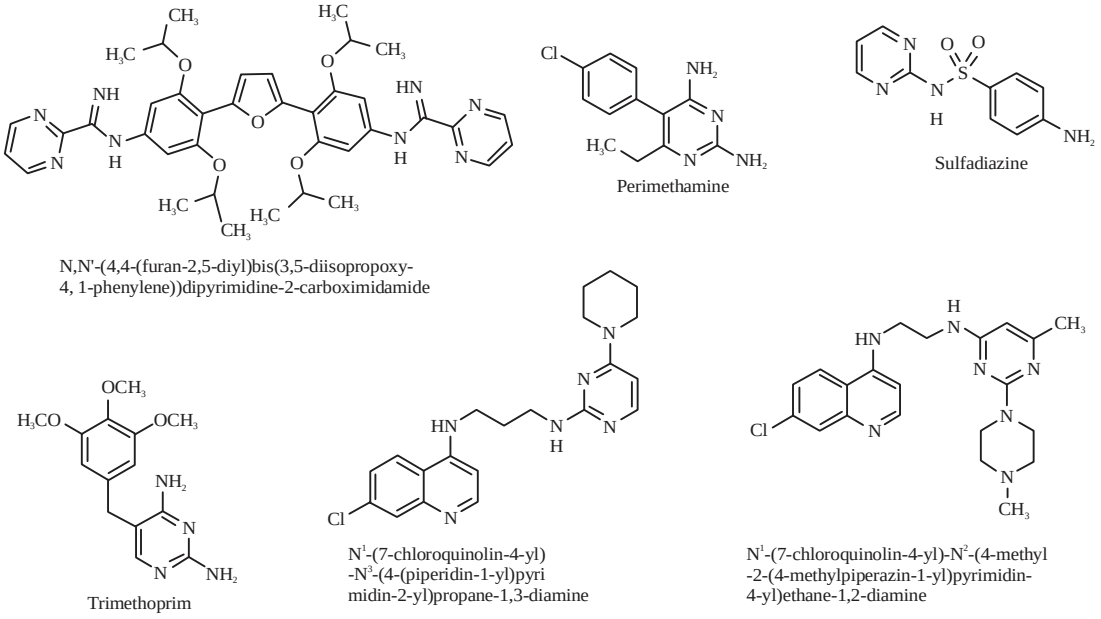


Fig. 44: Selected pyrimidine moieties with antimalarial activity

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)-1*H*-1,2,3-triazol-1-yl)methyl) benzenesulfonamide (Fang *et al*., 2015) and 3,4-dihydro-2*H*,6*H*-

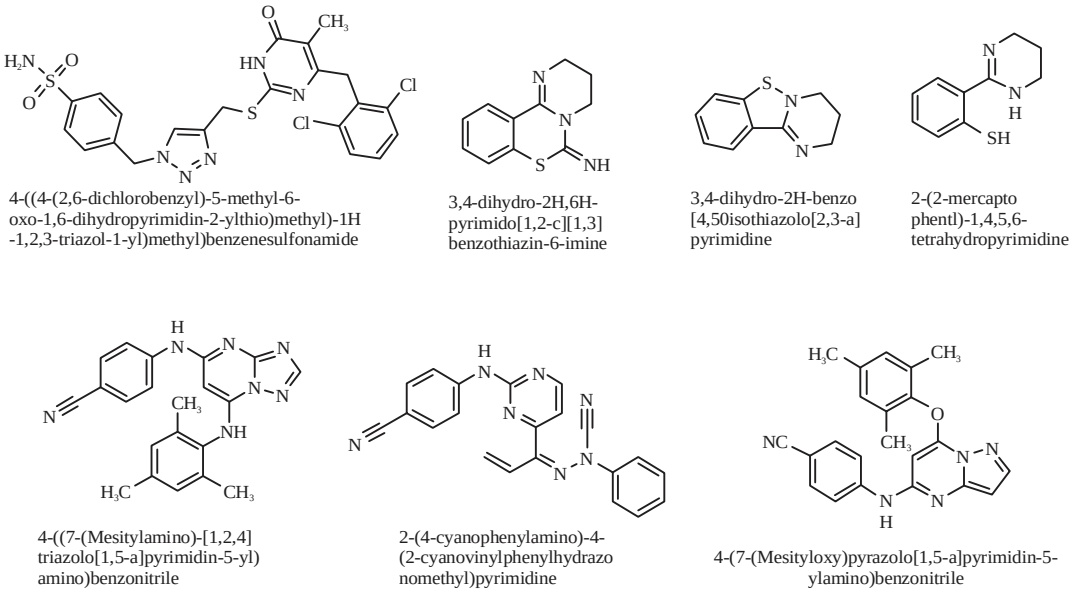
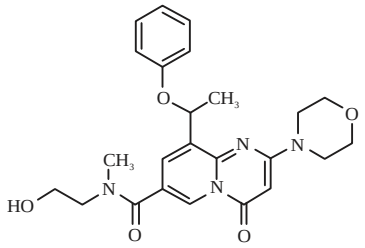


Fig. 45: Selected pyrimidine moieties with anti-HIV activity

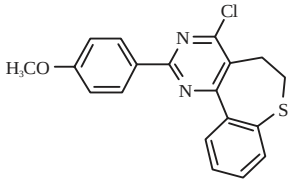
pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (Ghebremariam *et al*., 2014) as well as 3,4-dihydro-2*H*-benzo[4,5]isothiazolo[2,3-a]pyrimidine (Okazaki *et al*., 2015a), shown in Fig. 45, exhibited strong HIV-1 inhibitory potency at EC_{50} of 3.22, 0.30 and 0.29 μM, respectively. Chemical transformation of this isothiazolo- was achieved later to produce 2-(2-mercaptophenyl)-1,4,5,6-tetrahydropyrimidine (Fig. 45) which was un veiled 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) benzonitrilewas discovery 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-phenoxyethyl)-4*H*-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.

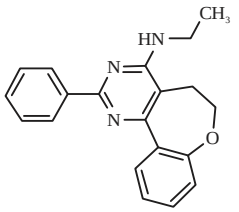
Kinase inhibitory activity: 2-(4-methoxyphenyl)-5-methyl-*N*-(4-methylphenyl)[1,3]oxazolo[5,4-*d*]pyrimidin-7-amine strongly inhibited VEGFR-2 kinase and HUVEC with IC_{50} values of 0.33 and 0.29 μM (Deng *et al*., 2015). (R)-5-chloro-N^2-[4-(4-methylpiperazin-1-yl)phenyl]-N^4-[(tetra hydrofuran-2-yl)methyl]pyrimidine-2,4-diamine 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)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine showed in



N-(2-hydroxyethyl)-N-methyl-2-morpholino -4-oxo-9-(1-phenoxyethyl)-4H-pyrido[1,2-a] pyrimidine-7-carboxamide

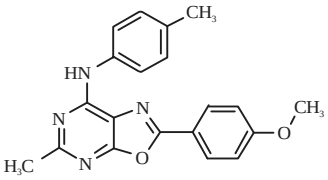


2-(4-methoxyphenyl)-4-chloro -5,6-dihydro[1]benzothiepino [5,4-d]pyrimidine

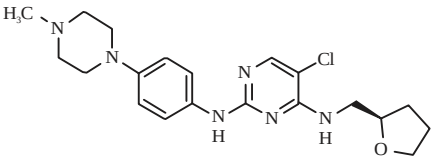


2-phenyl-4-ethylamino -5,6-dihydro[1]benzoxepino [5,4-d]pyrimidine

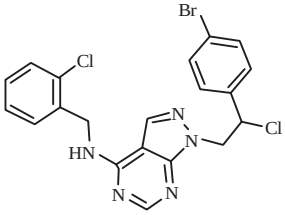
Fig. 46: Selected pyrimidine moieties with antiplatelet activity



2-(4-Methoxyphenyl)-5-methyl- N-(4-methylphenyl)[1,3]oxazolo [5,4-d]pyrimidin-7-amine

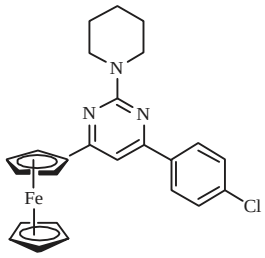


(R)-5-Chloro-N^2-[4-methylpiperazin- 1-yl)phenyl]-N^4-[(tetrahydrofuran-2- yl) methyl]pyrimidine-2,4-diamine

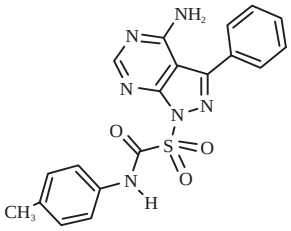


1-(2-(4-bromophenyl)-2-chloro ethyl)-N-(2-chlorobenzyl)-1H- pyrazolo[3,4-d]pyrimidin-4-amine

Fig. 47: Selected pyrimidine moieties with kinase inhibitory activity



4-(4-chlorophenyl)-6-ferrocenyl-2- piperidin-1-yl-pyrimidine



1-(4-amino-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-ylsulfonyl)-N-p-tolymethanamide

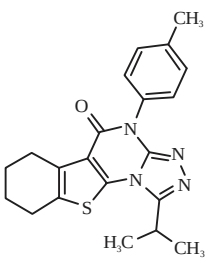
Fig. 48: Selected pyrimidine moieties with antitamoebic activity

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

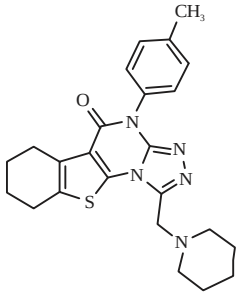
Antiamoebic activity: Amoebiasis, the most aggressive disease of the human intestine, is caused by the anaerobic protozoan parasite *Entamoeba histolytica* (Lejeune *et al*., 2009). Out of sixteen compounds evaluated against HM1: IMSS strain of *Entamoeba histolytica* by Parveen *et al.* (2010), 4-(4-chlorophenyl)-6-ferrocenyl-2-piperidin-1-yl-pyrimidine 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-1*H*-pyrazolo[3,4-d]pyrimidin-1-ylsulfonyl)-*N*-*p*-tolylme thanamide (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 pyrimidi nes 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]pyrimidin e-5(4*H*)-one, 4-(4-methylphenyl)-1-pyrrolidin-1-ylmethyl-6,7,8,9-tetrahydro[1,2,4]triazo lo[4,3-a]benzo(*b*)thieno[3,2-e]pyrimidine-5(4*H*)-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-(4 *H*)-one with the presented structures in Fig. 49, exhibited promising activities, which are comparable to the standard (Thore *et al*., 2015).

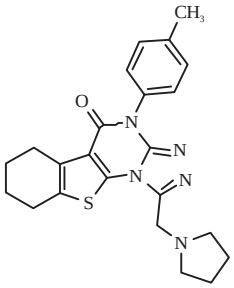
Herbicidal activity: Assay of a series of pyrimidine scaffolds designed by Cheng *et al.* (2015) for herbicidal activities revealed that 5-(4-chloro-2-fluoro-5-(prop-2-yn-1-yloxy)phenyl)-1,7-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione, with the structure shown in Fig. 50, exhibited significant herbicidal efficacy. 2-methyl-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-6-(prop-2-yn-1-yloxy)py rimidine 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)-1*H*-pyrazol-1-yl)-6-(prop-2-ynyloxy)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.



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

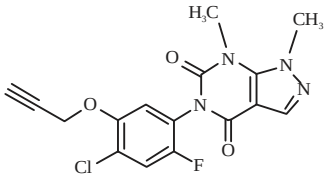


4-(4-methylphenyl)-1-pyrrolidin -1-ylmethyl-6,7,8,9-tetrahydro [1,2,4]triazolo[4,3-a]benzo(b)thieno [3,2-e]pyrimidine-5(4H)-one

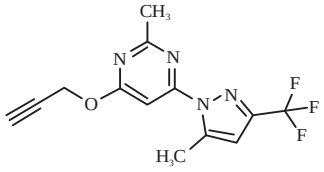


4-(4-methylphenyl)-1-piperidin -1-ylmethyl-6,7,8,9-tetrahydro [1,2,4]triazolo[4,3-a]benzo(b) thieno[3,2-e]pyrimidine-5(4H)-one

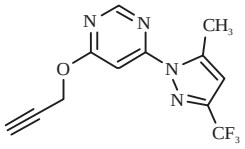
Fig. 49: Selected pyrimidine moieties with CSN depressant activity



5-(4-chloro-2-?uoro-5-(prop-2-yn-1 -yloxy)phenyl)-1.7-dimethyl-1H-pyra zolo[3,4-o]pyrimidine-4.6(5H,7H)-dione



2-mmethyl-4-[5-methyl-3-(trifluoro methyl)- 1H-pyrazol-1-yl]-6- (prop-2-yn-1-uloxy)pyrimidine



4-(5-methyl-3-(tri?uoromethyl) -1 H-pyrazol-1-yl)-6-(prop-2-yny loxy)pyrimidine

Fig. 50: Selected pyrimidine moieties with herbicidal activity

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 be 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.

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