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Review Article

A mini review of pyrimidine and fused pyrimidine marketed drugs

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Pyrimidine and its derivatives demonstrate a diverse array of biological and pharmacological activities including anticonvulsant, antibacterial, antifungal, antiviral and anticancer properties. This broad spectrum of biochemical targets has been facilitated by the synthetic versatility of pyrimidine, which has allowed the generation of a large number of structurally diverse derivatives including analogues derived from substitution of the aryl ring, and/or derivatisation of the pyrimidine nitrogen and C2/C4/C5/C6 carbon positions. Pyrimidines are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds and as raw material for drug synthesis. It was therefore the objective of this review to systematically evaluate the pharmacological properties of various substituted pyrimidine and collate these findings to be used as a guide for future structure-activity relationship and mode of action studies. This is the first review to comprehensively discuss the pyrimidine and its substituted derivatives.

Keywords: Pyrimidine, Marketed drugs.

Introduction

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Heterocycles (Katritzky *et al*. 1996) make up an exceedingly important class of compounds. In fact more than half of all known organic compounds are heterocycles. Many natural drugs such as quinine, papaverine, emetine, theophylline, atropine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes, luminophores, pesticides and herbicides are also heterocyclic in nature. One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures, with heterocyclic structures (Katritzky *et al*. 2008) receiving special attention as they

belong to a class of compounds with proven utility in medicinal chemistry (Martins *et al*. 2004). There are numerous biologically active molecules with six-membered rings, containing two hetero atoms. Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine **Fig 1**.

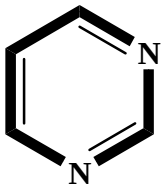


Fig 1 Pyrimidine

A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. An example of the last reaction type is the displacement of the amino group in 2-aminopyrimidine by chlorine and its reverse. Reduction in resonance stabilization of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions. One such manifestation is observed in the Dimroth rearrangement. Compared to pyridine, N-alkylation and N-oxidation is more difficult, and pyrimidines are also less basic: The pKa value for protonated pyrimidine is 1.23 compared to 5.30 for pyridine. Pyrimidines can also be prepared within the laboratory by organic synthesis. One method is the classic Biginelli reaction. The Biginelli reaction is a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1*H*)-ones from ethylacetoacetate, an aryl aldehyde (such as benzaldehyde), and urea **Fig 2**.

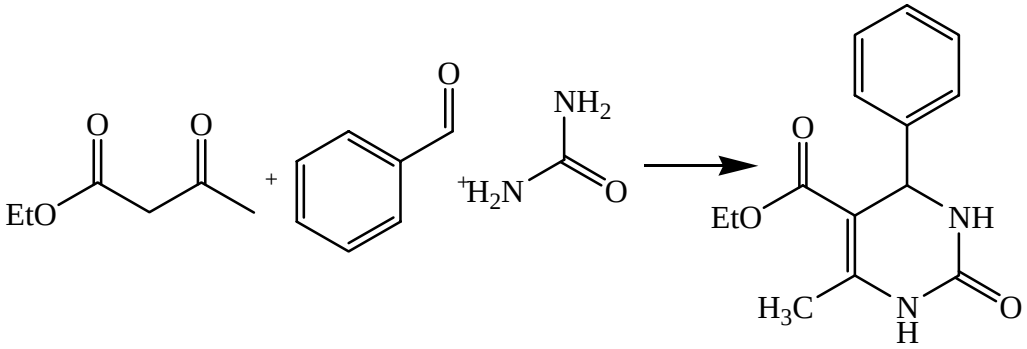


Fig 2. Biginelli reaction

This reaction was developed by Pietro Biginelli in 1891. The reaction can be catalyzed by Brønsted acids and/or by Lewis acids such as boron trifluoride. Several solid-phase protocols utilizing different linker combinations have been published. Dihydropyrimidinones, the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers, antihypertensive agents, and alpha-1-a-antagonists. Many other methods rely on condensation of carbonyls with amines for instance the synthesis of 2-Thio-6-methyluracil from thiourea and ethyl acetoacetate or the synthesis of 4-methylpyrimidine with 4,4-dimethoxy-2-butanone and formamide. A novel method is by reaction of certain amides with

Carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoro methanesulfonic anhydride **Fig 3**.

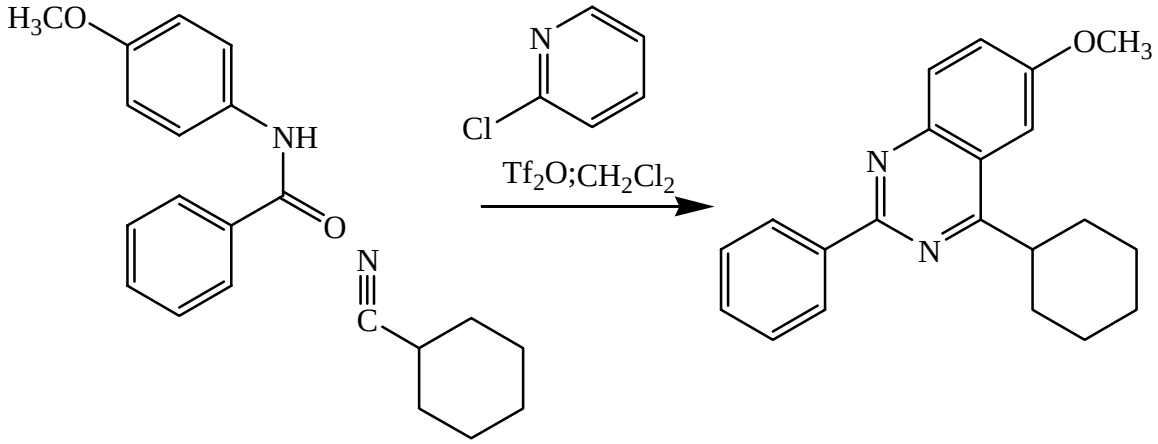
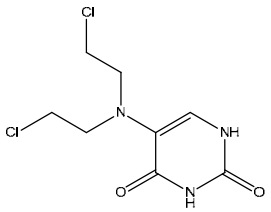


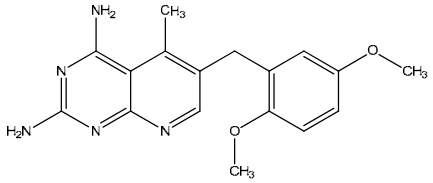
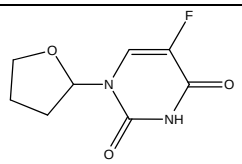
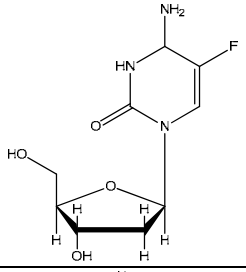
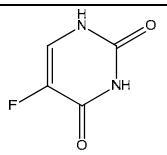
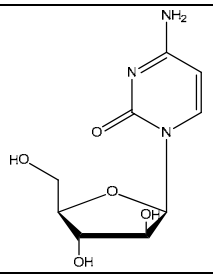
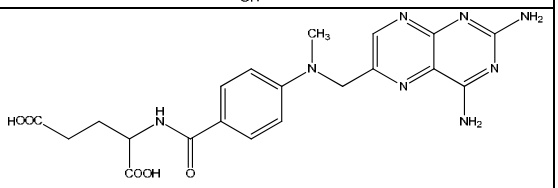
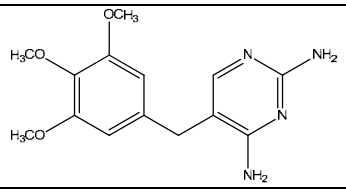
Fig 3. Electrophilic activation of the amide

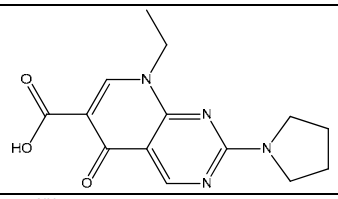
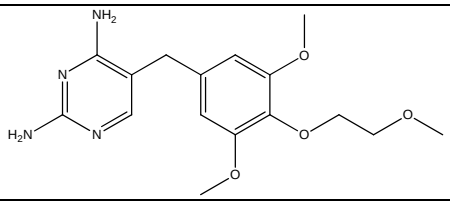
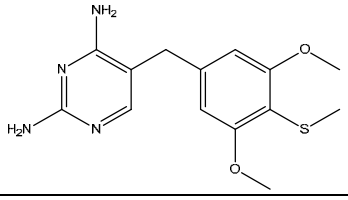
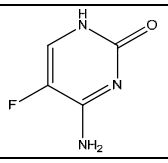
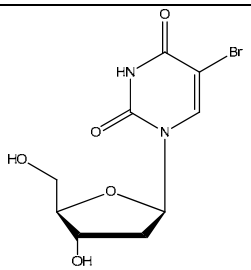
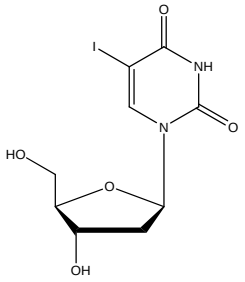
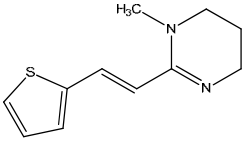
In the last several decades, fused pyrimidine derivatives is a class of heterocyclic compound that have attracted significant interest in medicinal chemistry as they have a wide range of pharmaceutical and pharmacological applications such as antineoplastic, antiviral, antibacterial, expectorant, urinary tract infection, parkinsonism, anthelmintic, vasodilator, liver disorder, infections of the respiratory tract and ear, treatment of gastrointestinal roundworms, peripheral neuropathies and disorders associated with hyperuricaemia.

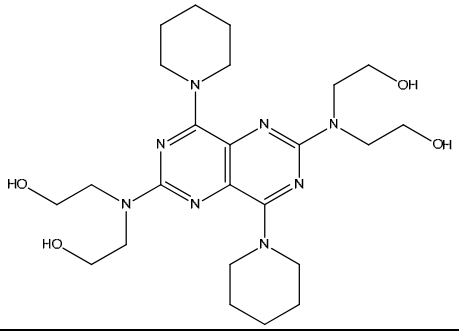
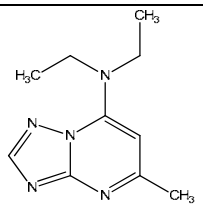
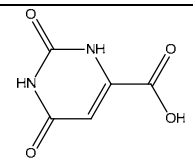
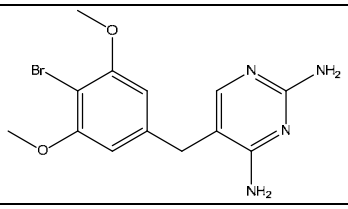
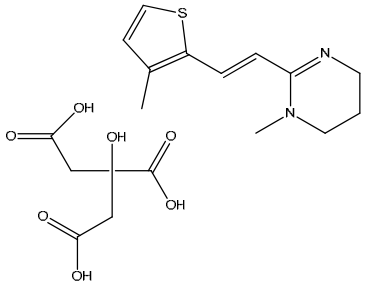
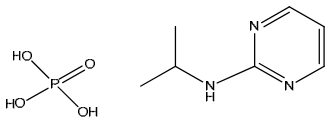
The fact that a majority of clinically active heterocyclic drugs possess a nitrogen hetero atomic system with one or two phenyl rings, at least one carbonyl group in their structure and presence of hydrogen donor/acceptor unit. In all of the pioneering experiments important core fragments (Bajda *et al*. 2007) is defined by presence of hydrogen donor/acceptor unit (HAD), hydrophobic domain (A) (aryl ring substituted/unsubstituted) and electron donor atom (D). This common features was found in the structures of well-established marketed drugs such as Uramustine, PiritreximIsetionate, Tegafur, Floxuridine, Fluorouracil, Cytarabine and Methotrexate etc., The pyrimidine and fused pyrimidine marketed drugs are tabulated in **Table 1**.

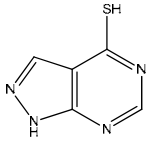
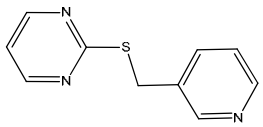
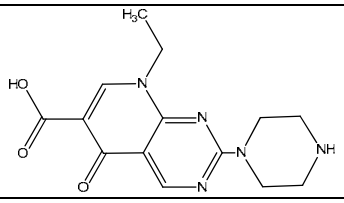
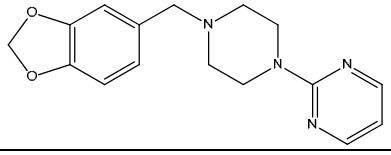
Table 1. List of Pyrimidine and fused pyrimidine marketed drugs

Antineoplastic		
Uramustine	5-Bis(2-chloroethylamino)uracil; [Bis(2-chloroethyl)amino]pyrimidine-2,4(1H,3H)-dione	

PiritreximIsetionate	2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d}pyrimidine mono(2-hydroxyethanesulphonate)	
Tegafur	5-Fluoro-1-(tetrahydro-2-furyl)uracil;5-fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1H,3H)-dione	
Floxuridine	2′-Deoxy-5-flurouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-d-ribofuranosyl)-5-fluoropyrimidine-2,4(1H,3H)-dione	
Fluorouracil	5-Fluoropyrimidine-2,4(1H,3H)-di-one	
Cytarabine	1-β-d-Arabinofuranosylcytosine; 4-Amino-1-β-d-arabinofuranosylpyrimidine-2(1H)-one	
Methotrexate	N-{4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl}-l-glutamic acid	
Antibacterial		
Trimethoprim	5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine	

Piromidic Acid	8-Ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-d]pyrimidine-6-carboxylic acid	
Tetroxoprim	5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyl-diamine	
Metioprim	5-(3,5-Dimethoxy-4-methylthiobenzyl-2,4,diyldiamine	
Antifungal		
Flucytosine	5-Fluorocytosine; 4-Amino-5-fluoropyrimidine-2(1H)-one	
Antivirals		
Broxuridine	5-Bromo-2′-deoxyuridine; 5-Bromo-1-(2-deoxy-β-d-ribofuranosyl)pyrimidine-2,4(1H,3H)-dione	
Idoxuridine	2′-Deoxy-5-iodouridine	
Anthelmintic		
Pyrantel Embonate	1,4,5,6-Tetrahydro-1-methyl-2[(E)-2-(2-thienyl)vinyl] pyrimidine 4,4′-methylenebis(3-hydroxy-2-naphthoate	

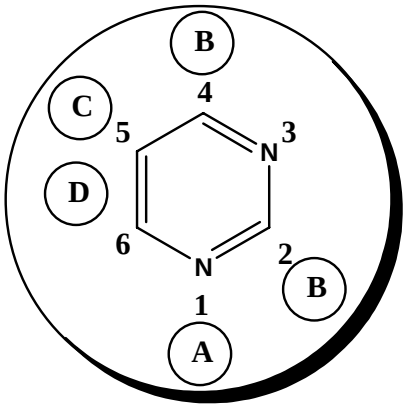
Vasodilators		
Dipyridamole	2,2′,2′′,2′′′-[(4,8-Dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetraethanol	
Trapidil	7-Diethylamino-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine	
Liver disorder		
Orotic Acid	1,2,3,6-Tetrahydro-2,6-dioxopyrimidine-4-carboxylic acid	
Respiratory tract and ear infections		
Brodimoprim	2,4-Diamino-5-(4-bromo-3,5-dimethoxybenzylpyrimidine	
Gastrointestinal roundworms infections		
Morantel Citrate	1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine citrate	
Peripheral neuropathies		
Isaxonine Phosphate	2-(Isopropylamino)pyrimidine phosphate	

Disorders associated with hyperuricaemia		
Tisopurine	1H-Pyrazolo[3,4-d]pyrimidine-4-thiol	
Expectorant and mucolytic		
Tasuldine	2[(3Pyridylmethyl)thio]Pyrimidine	
Urinary tract infections		
Pipemidic Acid	8-Ethyl-5,8-dihydro-5-oxo-2-(piperazin-1-yl)pyrido[2,3-d]pyrimidine-6-carboxylic acid	
Parkinsonism		
Piribedil	2-(4-Piperonylpiperazin-1-yl)pyrimidine	

In general, lipophilicity is one of the most important parameter because it is mainly involved in pharmacokinetic processes such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) and in ligand–target interactions (El-Baih *et al*. 2006). Lipophilicity is the molecular parameter of choice in numerous quantitative structure–activity relationships (QSAR) of different classes of compounds (Mossman, 1983). The promising activity of the compounds may be attributed to the substitutions at the hydrophobic domain. These marketed compounds contain substitutions and their positions are important core to produce pharmacological activities.

Structure Activity Relationships (SAR) study

As SAR studies give insights into the molecular properties causing receptor affinity and selectivity. The promising nature of the compounds may be attributed to the substitutions at the hydrophobic domain. These compounds had electron withdrawing and donating groups at the *ortho, meta* & *para* position of the hydrophobic aryl ring. In general it was observed that the substituted derivatives were more active than the other derivatives. This may be because of the fact that the substituted derivatives are better fitted into the receptor site. In all of the pioneering experiments important core fragments (Bruno-Blanch *et al*. 2003, Estrada and Pena, 2000) is defined by presence of hydrogen donor/acceptor unit (HAD), hydrophobic domain (A) (aryl ring substituted/unsubstituted) and electron donor atom (D). This common features was found in the structures of well-established pyrimidine drugs (**Fig 4**).



A Five membered saturated heterocyclic ring substitution leads to anticancer and antiviral activities

B 2nd position six or five membered saturated heterocyclic ring substitution leads to anthelmintic, antiparkinsonism expectorant and treatment of GI disturbance, peripheral neuropathies

B 2nd and 4th position keto group substitution or amino substitution or mixed keto, amino groups substitution leads to anticancer, antiviral, antibacterial, antifungal, and treatment of respiratory tract infection and liver disorder

C 5th position with halogen or substituted amine or saturated distal heterocyclic ring substitution leads to antibacterial and anticancer activities

D 5th and 6th position fused with heterocyclic ring and *o*, *m*, *p* substituted distal aryl ring substitution leads to anticancer, antiviral, antibacterial, vasodilation and treatment of urinary tract infection

Fig 4. SAR of pyrimidine marketed drugs

Conclusions

The article has outlined the biological activities of the pyrimidine scaffold. The biological activities of the pyrimidine indicates the maneuverability and versatility, which offer the medicinal chemist a continued interest in the pyrimidine skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules will ensure that this is an active and important area of research in heterocyclic chemistry.

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