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Demystifying the syntheses, anti-inflammatory activities and structure: Activity relationships of pyrimidines

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Abstract
Inflammatory effects of pyrimidines are attributed to their inhibitory response *versus* the expression and activities of certain vital inflammatory mediators namely prostaglandin E_2, inducible nitric oxide synthase, tumour necrosis factor-α, nuclear factor κB, leukotrienes, and some interleukins. Literature studies reveal that a large number of pyrimidines exhibit potent anti-inflammatory effects. SARs of numerous pyrimidines have been discussed in detail. Several possible research guidelines and suggestions for the development of new pyrimidines as anti-inflammatory agents are also given. Detailed SAR analysis and prospects together provide clues for the synthesis of novel pyrimidine analogy possessing enhanced anti-inflammatory activities with minimum toxicity. The trease5rcher found that Inflammation is biological feedback of the immune system that is initiated by several toxic stimuli, namely, microorganisms, chemical irritants, damaged cells, and noxious compounds. Inflammation acts via the elimination of all these harmful stimuli, and thus triggers the process of tissue repair. Nevertheless, chronic inflammations can cause severe disorders, for example, diabetes, hepatitis, asthma, cardiovascular diseases and rheumatoid arthritis.

Keywords: Anti-inflammatory activities, structure-activity, pyrimidines

Introduction
The word inflammation is derived from the Latin "*flamma"* meaning flame. It is normal feedback of the body to safeguard tissues against disease or infection. The inflammatory reaction initiates with the generation and discharge of chemical agents from the cells in the diseased, infected, or wounded tissue. Inflamed tissues produce extra signals that use leukocytes (white blood cells) at the position of inflammation. Leukocytes damage any infective or harmful agent and eliminate cellular residues from damaged tissue. This inflammatory reaction generally stimulates the curing process. However, an uncontrolled inflammatory response may become detrimental. Inflammation represents a portion of the body's immune response. An inflammatory reaction is liable for curing wounds, infections, and any damage to the tissues. Numerous feedbacks produced by the defines mechanism as a response to a physical injury or an infection result in inflammation.–Acute inflammation grows rapidly and turns out to be severe in a brief time. Its symptoms continue for a few days but may last for several weeks under certain circumstances. Common indications of acute inflammation include swelling, redness, pain, immovability, and heat. Acute inflammation can be caused by certain conditions and diseases including acute bronchitis, abrasion or cut on the skin, achy throat from flu or cold, infected ingrown toenail, acute appendicitis, sinusitis, tonsillitis, dermatitis, infective meningitis, high-intensity exercise, and physical trauma- Chronic inflammation persists for a prolonged duration (for several months and even years) in which active inflammation, tissue damage, and repair occur concurrently. Usually, the extent and effects of chronic inflammation differ with the source of the injury and the efficiency of the body to heal and control the damage. Chronic inflammation is characterized by typical symptoms such as body pain, fever, rash, weight gain or weight loss, fatigue, joint pain, and mouth sores. Chronic inflammation may lead to the progression of certain diseases namely diabetes, cancer, cardiovascular diseases, rheumatoid arthritis, allergies, chronic obstructive pulmonary disease (COPD), tuberculosis, asthma, hepatitis, periodontitis and chronic peptic ulcer.

Indicates the health complications associated with acute and chronic inflammations. Nonsteroidal anti-inflammatory drugs (NSAIDs *e.g.* ibuprofen, aspirin or naproxen), herbal supplements (*e.g.* curcumin, capsaicin, and *Boswellia serrata*) and corticosteroids (*e.g.* prednisone) can be utilized to lower the pain and fever resulting from numerous inflammatory disorders. Presently, NSAIDs are the most widely used to alleviate inflammatory fever and pain. The key mechanism of action of NSAIDs involves the suppression of the cyclooxygenase (COX) enzymes. COX enzymes are needed to convert arachidonic acid into thromboxanes, prostaglandins (PGE_2) and prostacyclins. The beneficial effects of NSAIDs are credited to the deficiency of these eicosanoids. Particularly, thromboxane's cause platelet adhesion, PGE_2 plays a role in vasodilation, enhances the temperature set-point in the hypothalamus, and lead to anti-nociception. Prostaglandins (PGE_2) are lipid compounds that are generated by COX enzymes in nearly every human tissue and are responsible for inducing inflammation *via* their role in vasodilation. Two isoforms of COX enzyme namely COX-1 and COX-2 are responsible for the generation of PGE_2 from arachidonic acid. NSAIDs inhibit the activity of COXs and thus reduce the amount of PGE_2 throughout the body. Consequently, existing inflammation, fever and pain are alleviated. Traditional NSAIDs act non-selectively by inhibiting both COX-1 and COX-2 enzymes. On the other hand, coxibs (celecoxib, rofecoxib and etoricoxib) represent a class of NSAIDs that selectively target the COX-2 without influencing COX-1. Coxibs possess anti-inflammatory effects similar to traditional nonselective NSAIDs, but there is some proof that they may be weaker analgesics. Important NSAIDs approved by Food and drug administration (FDA) include aspirin, diclofenac, etodolac, fenoprofen, flurbiprofen, indomethacin, ibuprofen, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac and tolmetin (Fig. SI-1†). However, the use of both traditional NSAIDs and coxibs has been linked with several adverse effects including cardiovascular and gastrointestinal (GI) disorders. They harm the upper and lower bowel by corroding COX-1 derived prostaglandins and producing local injury to the mucosa. Moreover, kidney toxicity has been reported in approximately 1-5% NSAIDs users. Among heterocycles, nitrogen-containing compounds represent an important class and have contributed substantially to the research field of medicinal chemistry.

Pyrimidines and their medicinal applications: Pyrimidine is an aromatic heterocyclic compound analogous to pyridine. It is one of the three diazines (unsaturated six-membered ring containing two nitrogen atoms) that has two nitrogen atoms at positions-1 and -3 in the ring. Heterocyclic compounds carrying pyrimidine rings are of enormous importance because they represent a vital family of natural and synthetic products, several of which display valuable clinical applications and bioactivities.

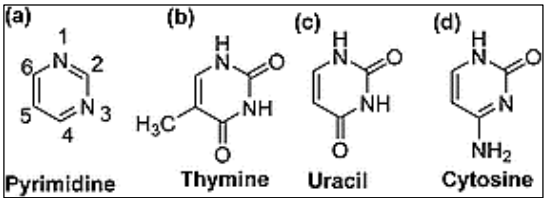


Fig 1: Chemical structures of (a) pyrimidine, (b) thymine, (c) uracil, and (d) cytosine

Substituted pyrimidines and purines are extensively found in living things and are among the leading compounds investigated by chemists. Pyrimidines represent the most abundant members of the diazine class with thymine uracil and cytosine being key components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Moreover, pyrimidine moiety occurs in several natural products, for instance, vitamin B_1 (thiamine) and various synthetic products, such as barbituric acid and veronal, which are used as soporific drugs (sleeping pills).

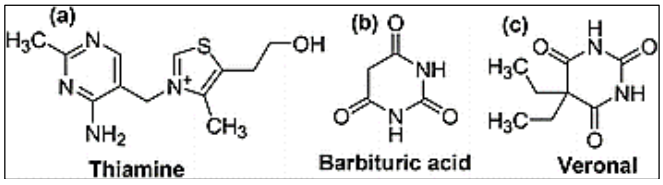
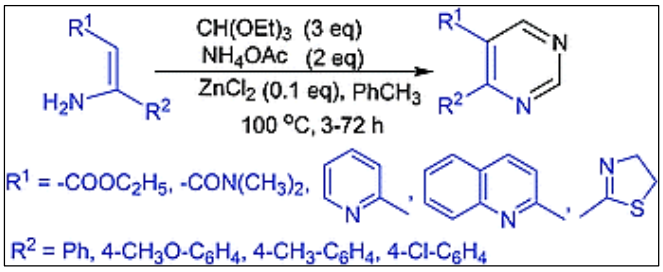


Fig 2 Chemical structures of (a) thiamine (b) barbituric acid, and (c) veronal

Literature survey indicates that pyrimidine derivatives demonstrate a variety of pharmacological activities (Fig. SI-2) comprising antifungal, antibacterial, analgesic, antileishmanial, antihypertensive, antiviral, antipyretic antidiabetic, antioxidant, anticonvulsant, antihistaminic and anti-inflammatory. However, literature related to the synthesis, anti-inflammatory activities and SAR studies of the pyrimidine derivatives is selected for this review.

Advances in the synthesis of pyrimidines: Pyrimidines have simple chemistry which facilitates several substitutions on their core ring through facile synthesis. Currently, numerous methodologies are used for the synthesis of pyrimidine analogy. A few of them are reported from the recent literature below.

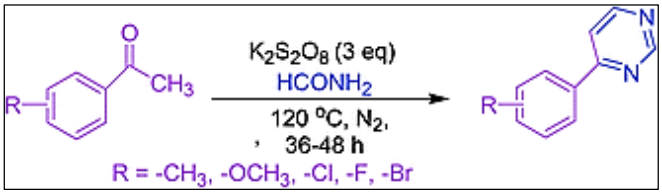
Synthesis *via* $ZnCl_2$-catalyzed three-component coupling reaction: A three-component coupling reaction comprising substituted enamines, triethyl orthoformate and ammonium acetate under $ZnCl_2$ catalysis yielded numerous 4,5-disubstituted pyrimidine analogs in a single step.



Scheme 1: Synthesis of 4,5-disubstituted pyrimidine analogy *via* $ZnCl_2$-catalyzed three-component coupling reaction

Synthesis *via* $K_2S_2O_8$-facilitated oxidative annulation reaction

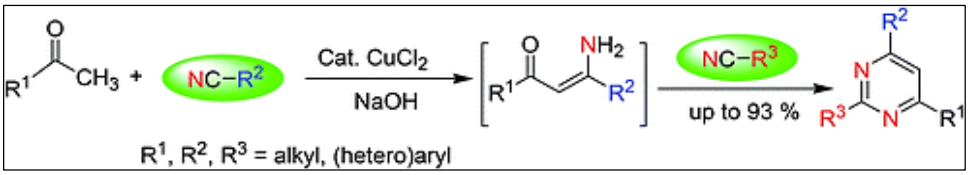
This approach consists of a $K_2S_2O_8$-facilitated oxidative annulation reaction involving formamide as a route towards pyrimidines. Activation of acetophenone-formamide conjugates resulted in the formation of 4-arylpyrimidines.



Scheme 2: Synthesis of 4-arylpyrimidines *via* $K_2S_2O_8$-facilitated oxidative annulation reaction

Synthesis *via* cyclization of ketones with nitriles

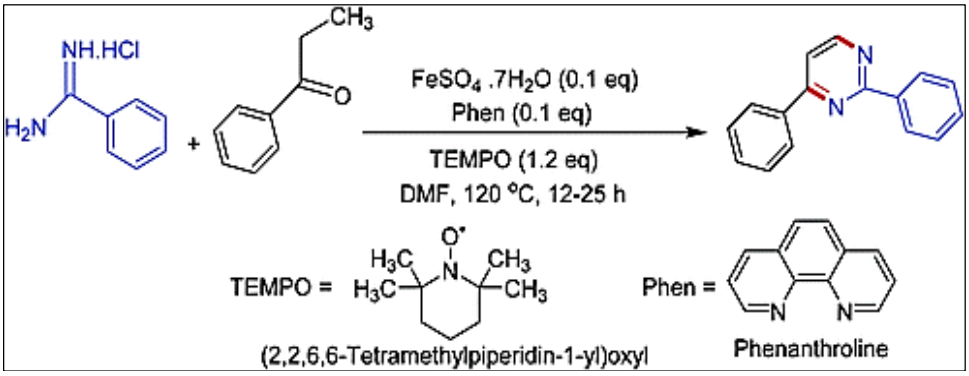
Distinctly substituted pyrimidines are synthesized *via* a simple and cost-efficient procedure that involves the cyclization of ketones with nitriles under Cu-catalysis in the presence of a base



Scheme 3 Pyrimidines synthesis *via* cyclization of ketones with nitriles under base catalysis.

Synthesis *via* the reactions of carbonyl compounds with amidines

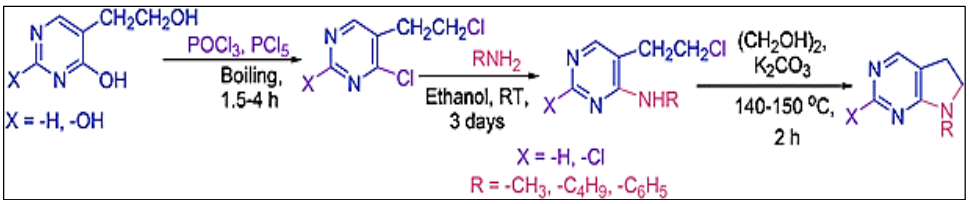
Synthesis of numerous pyrimidine analogy has been reported by the regioselective reaction of carbonyl compounds (esters, aldehydes and ketones) with amidines in the presence (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and an *in situ* prepared recyclable iron(ii)-complex. The mechanism indicated that the reactions progressed *via* a TEMPO complexation/enamine addition/transient α-occupation/β-TEMPO elimination/ cyclization order (Scheme 4).



Scheme 4: Pyrimidines synthesis *via* the reactions of carbonyl compounds with amidines

Synthesis of 5-substituted pyrimidine derivatives

The chemical characteristics and reactivities of 4-hydroxy- and 2,4-dihydroxy-5-(β-hydroxyethyl) pyrimidine derivatives, and the products of their modifications have been investigated. In the first step of the synthetic approach (Scheme 5), 4-chloro-and 2,4-dichloro-5-(β-chloroethyl) pyrimidine analogy were obtained. In the next step, the synthesis of several 4-alkyl(aryl)amino-5-(β-chloroethyl) pyrimidine derivatives was reported, which were subsequently transformed into 5,6-dihydropyrrolo[2,3-*d*] pyrimidine derivatives (Scheme 5.



Scheme 5: Synthesis of 5,6-dihydropyrrolo[2,3-*d*] pyrimidines

Synthesis in the anti-inflammatory activities of pyrimidines

Owing to the noteworthy pharmacological potential of pyrimidine derivatives, extensive research has been directed to their anti-inflammatory effects. Several pyrimidine analogs such as afloqualone, proquazone, epirizole and

tofacitinib (Fig. 3) have already been approved as anti-inflammatory drugs and are in clinical use.

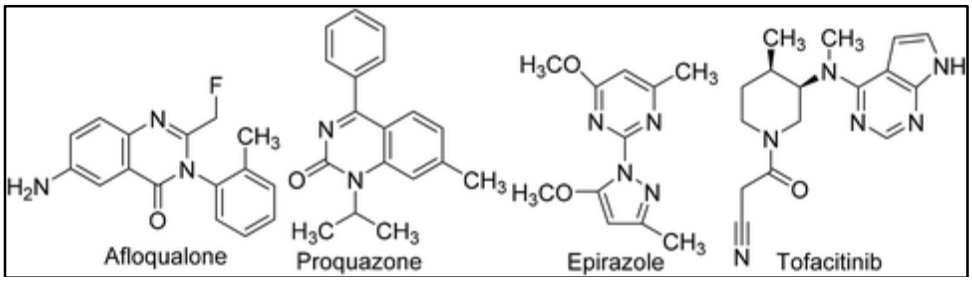


Fig 3: Clinically used pyrimidine-based anti-inflammatory drugs

Numerous research teams described the anti-inflammatory effects of various synthetic and natural pyrimidines. Their findings suggest that pyrimidines exhibit anti-inflammatory effects by inhibiting vital inflammatory mediators such as PGE_2, nitric oxide (NO), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), chemokines, and cytokines. Consequently, this section of the article is focused on the inhibitory effects of pyrimidine derivatives against some key inflammatory mediators.

Table 1: Anti-inflammatory activities of compounds (60-63) (reproduced with permission from O. I. Abd El-Salam, *et al.*, Egypt. J. Chem., 2012, 55, 529-547, © 2012, Egyptian Chemical Society)

Compound no.	Anti-inflammatory activity		
	Dose, mg kg^{-1} p.o.	% inhibition of oedema	% inhibition of PGE_2
60	2.5	80.55	90.98
	5	89.35	96.89
61	2.5	85.32	83.98
	5	91.06	90.00
62	2.5	82.98	77.98
	5	87.98	86.00
63	2.5	94.20	85.31
	5	95.88	92.09
Diclofenac potassium	2.5	81.09	75.89
	5	85.44	84.87

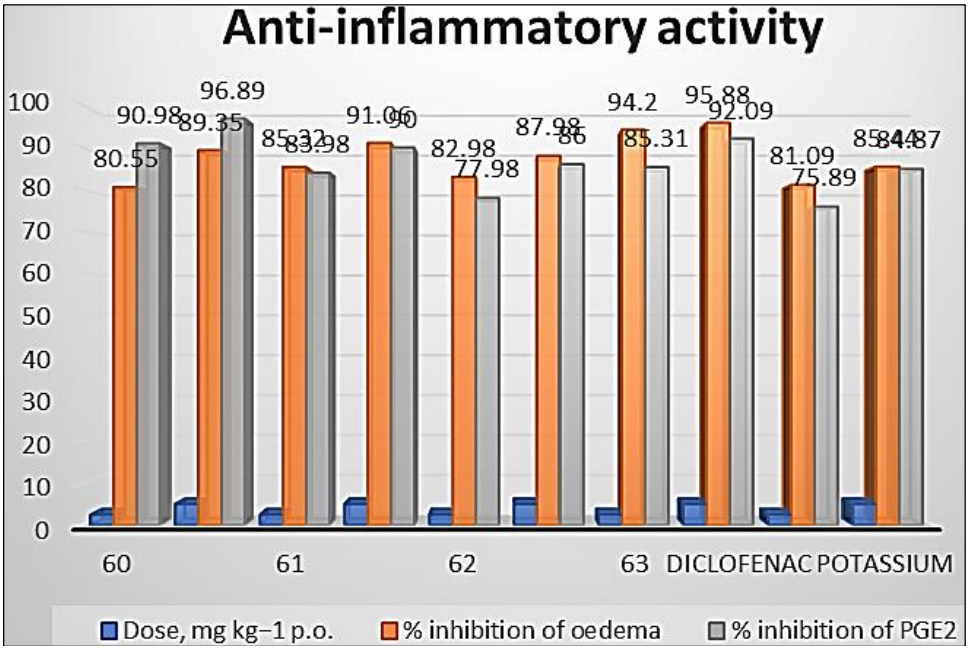


Fig 5: Showing the graphical representation of anti-inflammatory activities of compounds (6063)

Bakr *et al.* reported the synthesis of several new 1-phenylpyrazolo pyrimidine analogy. The target compounds were screened for their COXs enzymes inhibitory effects and anti-inflammatory activities *via* an EIA kit and *in vivo* carrageenan-induced paw edema method in rats, respectively. Preliminary data indicated that all the tested analogs displayed stronger inhibitory effects *versus* COX-2 enzyme (IC_{50} = 0.56-5.89 μM) than COX-1 enzyme (IC_{50} = 3.97-10.11 μM). SAR study revealed that the derivatives carrying a pyrazolyl scaffold in a hybrid configuration with

the pyrazolo[3,4-*d*] pyrimidine moiety (64-69) were typically stronger inhibitors of COX-2 enzyme than the compounds having other scaffolds. Moreover, the six hybrids were also noticed to be more COX-2 selective. The 4,5-dimethylpyrazole analog was observed to be the strongest COX-2 inhibitor (IC_{50} = 0.56 μM), whereas the 5-aminopyrazole analog (65) as noticed to be the most COX-2 selective (SI = 11.99). Moreover, all the six-analogy containing pyrazolyl moiety (64-69) and the acetohydrazide analogy (70) exhibited noteworthy anti-inflammatory effects (ED_{50} = 87.9-10.1 μmol kg^{-1}).

Conclusions

Inflammation is biological feedback of the immune system that is initiated by several toxic stimuli, namely, microorganisms, chemical irritants, damaged cells, and noxious compounds. Inflammation acts *via* the elimination of all these harmful stimuli, and thus triggers the process of tissue repair. Nevertheless, chronic inflammations can cause severe disorders, for example, diabetes, hepatitis, asthma, cardiovascular diseases, and rheumatoid arthritis. Presently, several NSAIDs are utilized to cure inflammatory disorders. Pyrimidines represent a group of aromatic heterocyclic compounds, enclosing two nitrogen atoms at positions-1 and -3 of the main six-member ring. They occur abundantly in natural as well as synthetic products and demonstrate a variety of pharmacological effects namely antibacterial, anti-inflammatory, antiviral, antifungal, and antitubercular activities. Several procedures for the synthesis of pyrimidines are described. Pyrimidines act as anti-inflammatory agents by suppressing the expressions and activities of inflammatory mediators. The inhibitory action of pyrimidine derivatives *versus* inflammatory mediators namely PGE_2, NO, NF-κB, IL-1β, IL-6, TNF-α, and leukotrienes are explained. The potential use of various pyrimidine derivatives as anti-inflammatory agents is expected owing to their high potency and minimum toxicity. SAR studies of various pyrimidine derivatives are discussed in detail.

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