


# One-pot and two-pot methods for chalcone derived pyrimidines synthesis and applications

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## Abstract

Chalcone-derived pyrimidine is a well-known heterocyclic compound that is commonly present in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) bio-isosteres. Pyrimidine derivatives are effective in both the electronic industry and drug industries. This review highlights the synthesis of pyrimidines, namely mono-pyrimidine, bis-pyrimidine, fused pyrimidine, symmetric, and asymmetric pyrimidine via one-pot and two-pot methods. The one-pot method is the direct reaction of amino derivatives with aldehydes and acetophenones, whereas the two-pot method is frequently reported for the synthesis of chalcone before the cyclization to a pyrimidine. This review is important in organic synthesis, particularly in the heterocyclic field, regarding pyrimidines and their significance in therapeutic and electronic industries.

## 1 | INTRODUCTION

Pyrimidine is an essential six-membered substance of heterocyclic chemistry<sup>[1,2]</sup> that belongs to the alkaloids family.<sup>[3]</sup> It contributes a significant role in several biological processes as vitamins, nucleic acid, purine, cytosine, uracil, thymine, folic acid, and coenzymes.<sup>[4–7]</sup> Pyrimidine is known as a cyclic amine of 1,3-diazine or *m*-diazine,<sup>[8]</sup> having a symmetrical structure with two nitrogen atoms at 1 and 3 positions.<sup>[9]</sup> Pyrimidine consists of nine hydrogenated derivatives, namely one hexahydropyrimidine, three tetrahydropyrimidines, and five dihydropyrimidines (Figure 1). The pyrimidine selection has numerous oxidation states, excluding tautomerization or ring conformational isomers. Whereas, mercapto, hydroxyl, and amino-substituted pyrimidine exhibited tautomerization at 2,4,6 position with thio, oxo, and imino groups.<sup>[10,11]</sup>

The chemistry of pyrimidines has been broadly studied as pharmacophore,<sup>[12]</sup> and chromophore.<sup>[13]</sup> moiety due to their potential and applications in electrochromic, solvatochromic, optical, photochromic,<sup>[14]</sup> anti-corrosive,<sup>[15]</sup> chemosensor,<sup>[16]</sup> optoelectronics or organic light-emitting diodes,<sup>[17]</sup> and photoproduct of DNA.<sup>[18]</sup> In therapeutic industry, pyrimidine derivatives have also been reported to

have a broad spectrum of biological properties, that is, anticancer,<sup>[19–30]</sup> antihistamine,<sup>[31,32]</sup> antinociceptive,<sup>[33]</sup> antilipase,<sup>[34]</sup> antifilarial,<sup>[35]</sup> antiparasitic,<sup>[36]</sup> antioxidant,<sup>[37,38]</sup> antituberculosis,<sup>[39,40]</sup> antihypertensive,<sup>[41]</sup> antimicrobial,<sup>[42–47]</sup> anticonvulsant,<sup>[48,49]</sup> antiallergic,<sup>[50,51]</sup> antipyretic,<sup>[52]</sup> anti-inflammatory,<sup>[53,54]</sup> antifungal,<sup>[55,56]</sup> antiviral,<sup>[57–59]</sup> antibacterial,<sup>[60]</sup> antimalarial,<sup>[61]</sup> anti-HIV,<sup>[62,63]</sup> antiulcer,<sup>[64]</sup> insecticide,<sup>[65]</sup> antineoplastic,<sup>[66]</sup> antiepileptic,<sup>[67]</sup> analgesic,<sup>[68]</sup> and anthelmintic.<sup>[69]</sup> Several commercially available drugs derived from pyrimidine are sildenafil (viagra), formycin A,<sup>[70]</sup> sulfadiazine,<sup>[71]</sup> pyrimethamine,<sup>[72]</sup> roscovitine,<sup>[73]</sup> indiplon, zaleplon,<sup>[74]</sup> ocinaplon,<sup>[75]</sup> dinaciclib,<sup>[75]</sup> fluoroestrone,<sup>[76]</sup> 5-fluorouracil,<sup>[77]</sup> ispinesib,<sup>[78]</sup> volasertib,<sup>[79]</sup> pictilisib, monastrol,<sup>[80]</sup> and etravirine<sup>[81]</sup> (Figure 2).

Pyrimidine can be synthesized from various methods.<sup>[82]</sup> such as (1) coupling isomerization and cyclocondensation of propargyl alcohol, aryl halides, and amidinium salts,<sup>[83]</sup> (2) one-pot condensation of ethylacetoacetate, barbituric acid, hydrazine hydrate, aromatic aldehydes,<sup>[84]</sup> (3) one-pot multi-components reaction of benzaldehyde, malononitrile, hydrazine hydrate, 4,4-dimethyl-3-oxopentenenitrile,<sup>[74]</sup> and (4) chalcone cyclization.<sup>[85]</sup> in acidic or basic media with urea