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Mini Review on Synthesis of Pyrimidinthione, Pyrimidinedione Derivatives and Their Biological Activity

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Abstract

The chemistry of heterocycles has received amongst the chemicals prominent attention in recent years owing to its importance in the pharmaceutical sector. Organic compounds carrying pyrimidinthione, pyrimidinedione, pyridazine rings have been reported to demonstrate a wide range of pharmacological activities, which includes antibacterial, antimicrobial, antioxidant, anti-HIV and anticancer activity. These observations have been guiding for the synthesis of various derivatives of these compounds enclosing biologically active nuclei and study their pharmacological activities.

Keywords: Chalcone; Pyrimidinthione; Pyrimidinedione; Biological activities

Introduction

Over the past decade the evolution of organisms resistant to nearly all the class of antimicrobial agents has become a severe public health concern [1,2]. Heterocyclic compounds have received considerable attention owing to their synthetic and biological importance in the enhancement of the quality of human life. Among numerous heterocycles compounds that have been synthesized and evaluated for their pharmacological activities, chalcone, pyrimidinone and pyrimidinethione have played a crucial role in medicinal chemistry. It was demonstrated that the presence of reactive α, β-unsaturated keto function in chalcones was responsible for their antibacterial and antifungal activities [3].

The pyrimidinones compounds have gained interest in recent years due to their wide-ranging biological activity. These compounds displayed therapeutic applications, as anticancer [4,5], antihypertensive [6], hypoglycaemic [7], antiviral [8], anticonvulsive [9], anti-inflammatory and analgesic [10] drugs.

On the other hand, literature surveys revealed that pyrimidinethione derivatives are an important class of heterocyclic molecules possessing a wide variety of biological properties. In fact, different studies demonstrated that various compounds possessing pyrimidinethione nucleus exhibited broad range of biological activities such as antimicrobial [11-13], antioxidant and antitumor activities [14], antitubercular [15] and hypoglycemic activity [16]. The current mini review aims to focus on some synthetic procedures of pyrimidinones and pyrimidinethione derivatives to facilitate the development of new heterocyclic compounds with more efficient and promising pharmacological activities.

Result and Discussion

Pyrimidinedione derivatives were synthesized from various arylmethylene acetophenone derivatives [17]. The chalcone derivatives were prepared using substituted ketone and distinct substituted benzaldehyde through condensation reaction. Likewise, pyrimidinedione derivatives (4) were synthesized via reaction between aryl methylene derivatives and/ or chalcones with thiourea and KOH in ethanol (50ml) in microwave oven for sufficient time and under an appropriate temperature. The detailed steps used in the synthesis of the pyrimidinedione derivatives were described in the literature [18].

The pyrimidine-2-thione derivatives (4) were screened in-vitro against gram positive and gram-negative strains and were found to be less active against the gram-positive bacteria in comparison with the minimal required dose for the action against the gram-negative bacteria in most cases [17] (Figure 1) (Table 1).

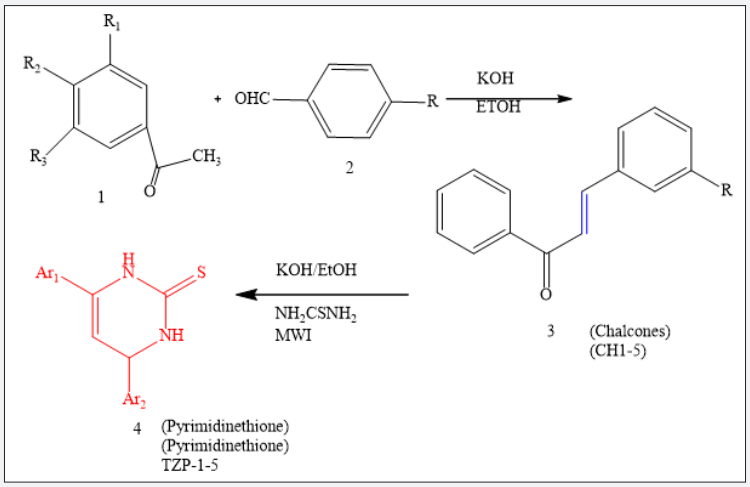

Figure 1: The synthesis of pyrimidinethiones [17].

Table1: List of the prepared chalcones [17].

Compound name	Ketones	Aldehydes
CH-1	Acetophenone	Benzaldehyde
CH-2	Acetophenone	p- dimethylaminobenzaldehyde
CH-3	2-hydroxyacetophenone	p-dimethylaminobenzaldehyde
CH-4	2-4-dihydroacetophenone	p-dimethylaminobenzaldehyde
CH-5	2-hydroxyacetophenone	benzaldehyde

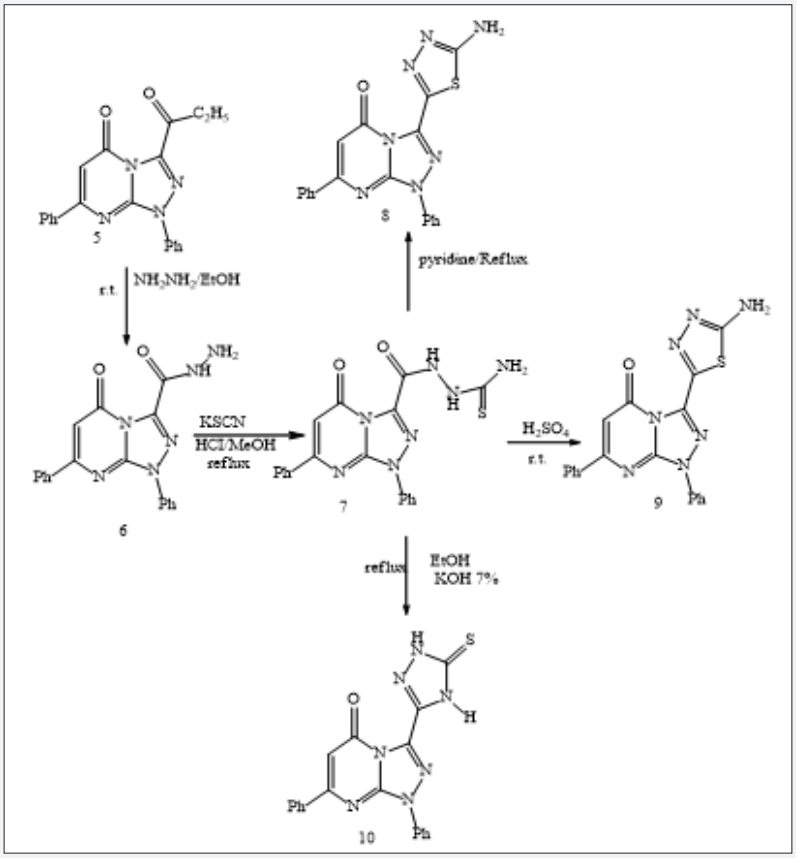

Figure 2: Synthesis of compounds 8, 9, 10[20].

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Ethyl 1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo [4,3-a] pyrimidine-3-carboxylate (5) was treated with hydrazine hydrate, in refluxing ethanol to give the corresponding acid hydrazide (6) in good yield [19,20]. Acid hydrazide (6) was treated with potassium thiocyanate in refluxing methanol, in the presence of hydrochloric acid to produce1-(1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo[4,3-a] pyrimidine-3-carbonyl) thiosemicarbazide (7). Compound (10) 3-(5-mercapto-4H-1,2,4-triazol-3-yl)-1,7-diphenyl-1,2,4-triazolo [4,3-a] pyrimidin-5-(1H)-one (10) was prepared by oxidative cyclization of compound (7) in basic medium (7% KOH) under reflux with subsequent acidification. It was found that further reflux of compound (7) with dry pyridine gave a product identified as 3- (5-amino-1,3,4-oxadiazol-2-yl)-1,7-diphenyl-1,2,4-triazolo [4,3-a]pyrimidin-5-(1H)-one (8) (Figure 2).

On the other hand, the reaction involving the synthesis of 1,7-diphenyl-3-(5-amino-1,3,4-thiadiazol-2-yl)-1,2,4-triazolo [4,3-a] pyrimidin-5-(1H)-one (9) took place through a dehydrative cyclization by reacting compound (3) with conc. sulfuric acid. The resulting product (9) was separated as green solid, and was slightly soluble in most organic solvents (Figure 2). Acid hydrazide (6) reacted with phenyl isothiocyanate in refluxing ethanol to produce 1-(1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo[4,3-a] pyrimidine-3-carbonyl) phenylthiol semicarbazide (11).

Besides, acid hydrazide (6) was treated with phenyl isothiocyanate in refluxing ethanol to give compound (11)1-(1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo [4,3-a] pyrimidine 3 carbonyl) phenyl thiosemicarbazide as shown in Figure 3. The latter product was subjected to intramolecular cyclization when treated with sulfuric acid, dry pyridine and KOH (5%) demonstrating a new synthetic route to produce compounds 12, 13 and 14, respectively. Subsequent treatment of compound (14) with methyl iodide in the presence of sodium ethoxide solution, yielded 3-(5-methyl thio-4-phenyl-4H-1,2,4-triazol-3-yl)-1,7-diphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5-(1H)-one (15). It is worth noting that the treatment of compound (14) or (15) with hydrazine hydrate under reflux condition produced the same product, identified as 3- (5-hydrazino-4-phenyl-4H-1,2,4-triazol-3-yl)-1,7-Diphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5(1H)-one (16) (Figure 3).

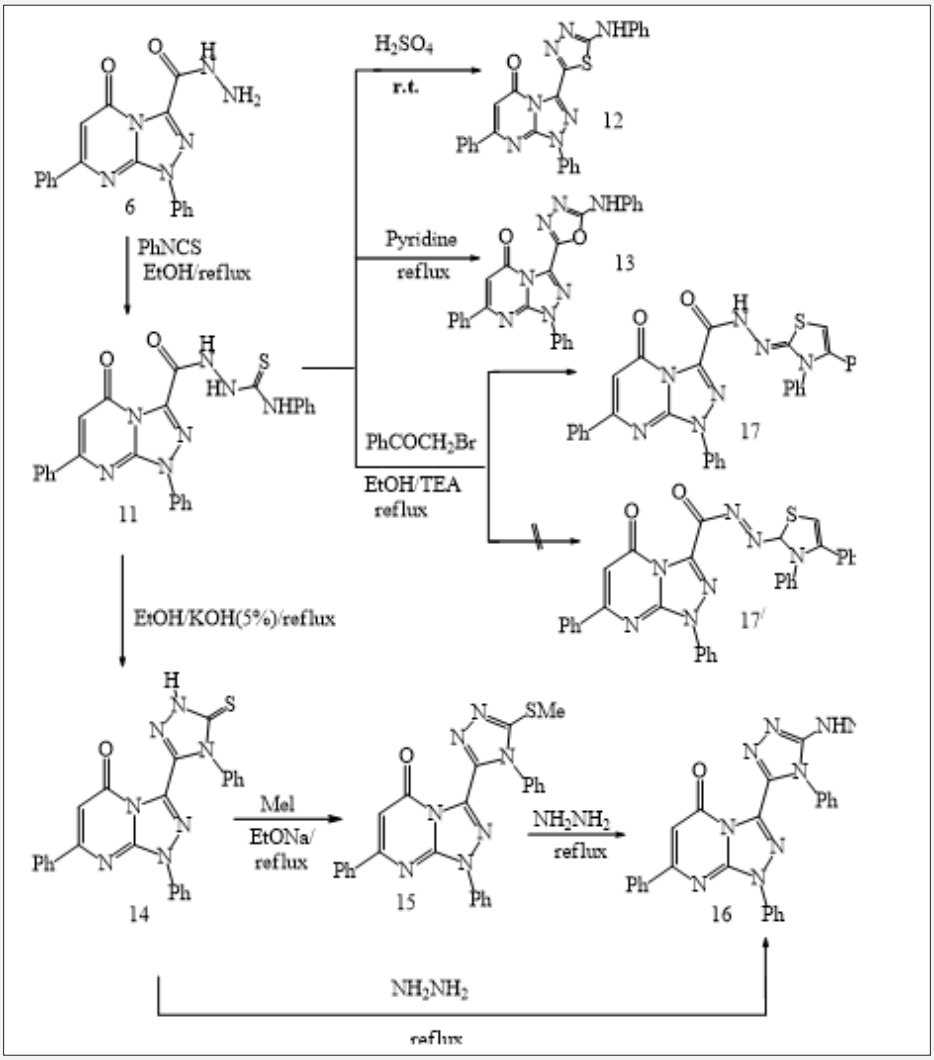

Figure 3: Synthesis of compounds 12, 13, 14,15,16,17.

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Besides, the treatment of compound (11) with phenacyl bromide in refluxing ethanol, in the presence of triethylamine, yielded 1,5-dihydro-5-oxo-1,7-dipheny-lN-(3,4-diphenyl-3H-thiazol-(2E)-ylidene-1,2,4-triazolo[4,3-a] pyrimidine-3-carbohydrazide (17) as shown in Scheme 3. Treatment of acid hydrazide (6) with carbon disulfide in ethanol, in the presence of potassium hydroxide at room temperature, resulted in the formation of potassium salt (18). The latter product reacted with ethanolic potassium hydroxide to afford 3-(5-mercapto-1,3,4-oxadiazole-2-yl)-1,7-diphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5(1H)-one (19) (Figure 3). The mechanism of formation of the corresponding ox diazole (19) was studied and discussed in previous studies [21-23]. Moreover, potassium salt (18) was subjected to treatment with hydrazine hydrate, in refluxing ethanol, the reaction yielded as 3-(5-mercapto-4-amino-4H-1,2,4-triazol-3-yl)-1,7-diphenyl-1,2,4-triazolo[4,3-a] pyrimidin-5(1H)-one (17) (Figure 3).

Additionally, it was reported that the reaction involving the synthesis of 4-amino-1, 2, 4-triazole can took place by a simple conversion of 1, 3, 4-oxadiazole under the action of hydrazine hydrate [24,25]. Likewise, the corresponding dicarbonyl compounds including acetylacetone and ethyl acetoacetate were subjected to condensation with acid hydrazide (6) in the presence of an appropriate amount of piperidine as catalyst to give the substituted pyrazole derivatives 3-(3,5-dimethylpyrazole-1-carbonyl)-1,7-diphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5(1H)-one (20) and 3-(3-methylpyrazole-5-oxo-1-carbonyl)-1,7-diphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5(1H)-one (21), respectively (Figure 4).

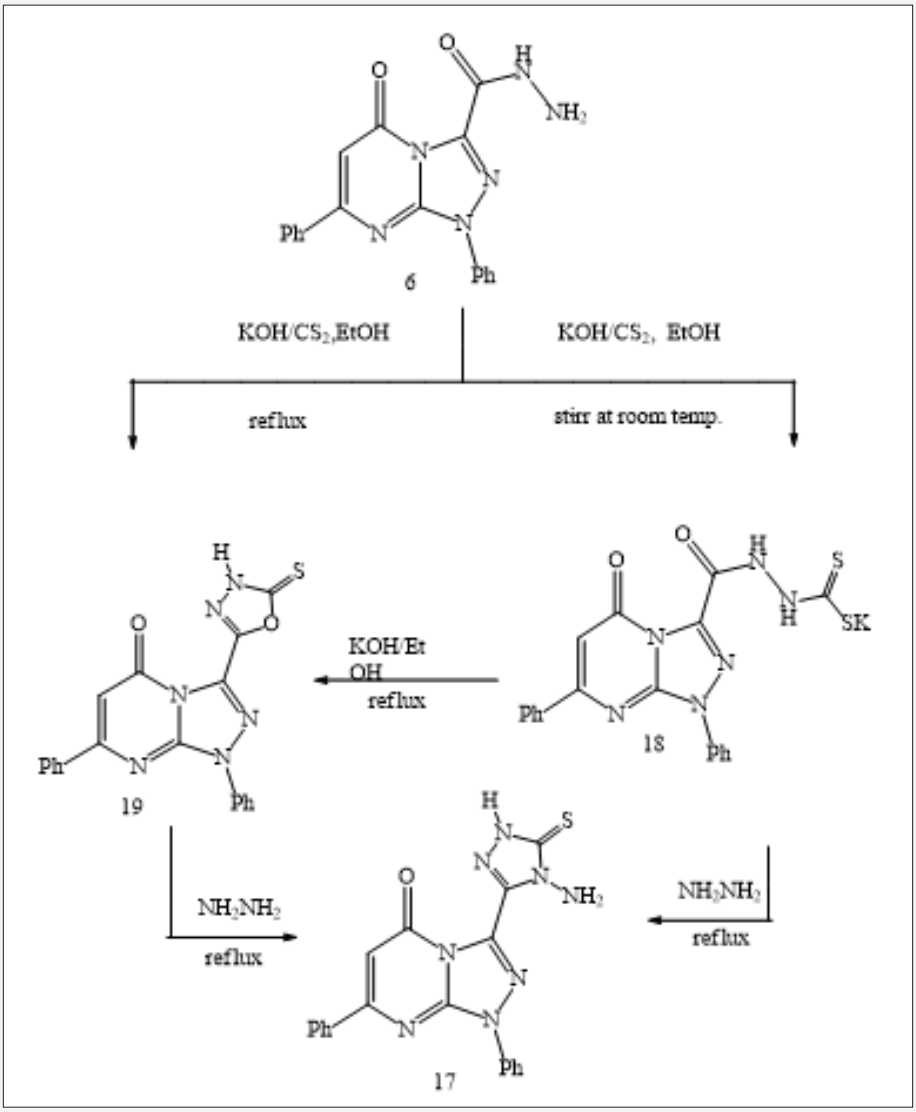

Figure 4:

The structure of these compounds was established based on spectral and elemental analysis reported in the related literature [26-28]. Finally, condensation of acid hydrazide (6) with acid anhydrides, namely phthalic anhydride and 2, 3, 4, 5-tetrachlorophthalic anhydride, in refluxing glacial acetic acid, produced the corresponding imides (22) and (23), respectively (Figure 4). Biological studies demonstrated that these compounds exhibited antihypertensive activity [20] (Figure 5).

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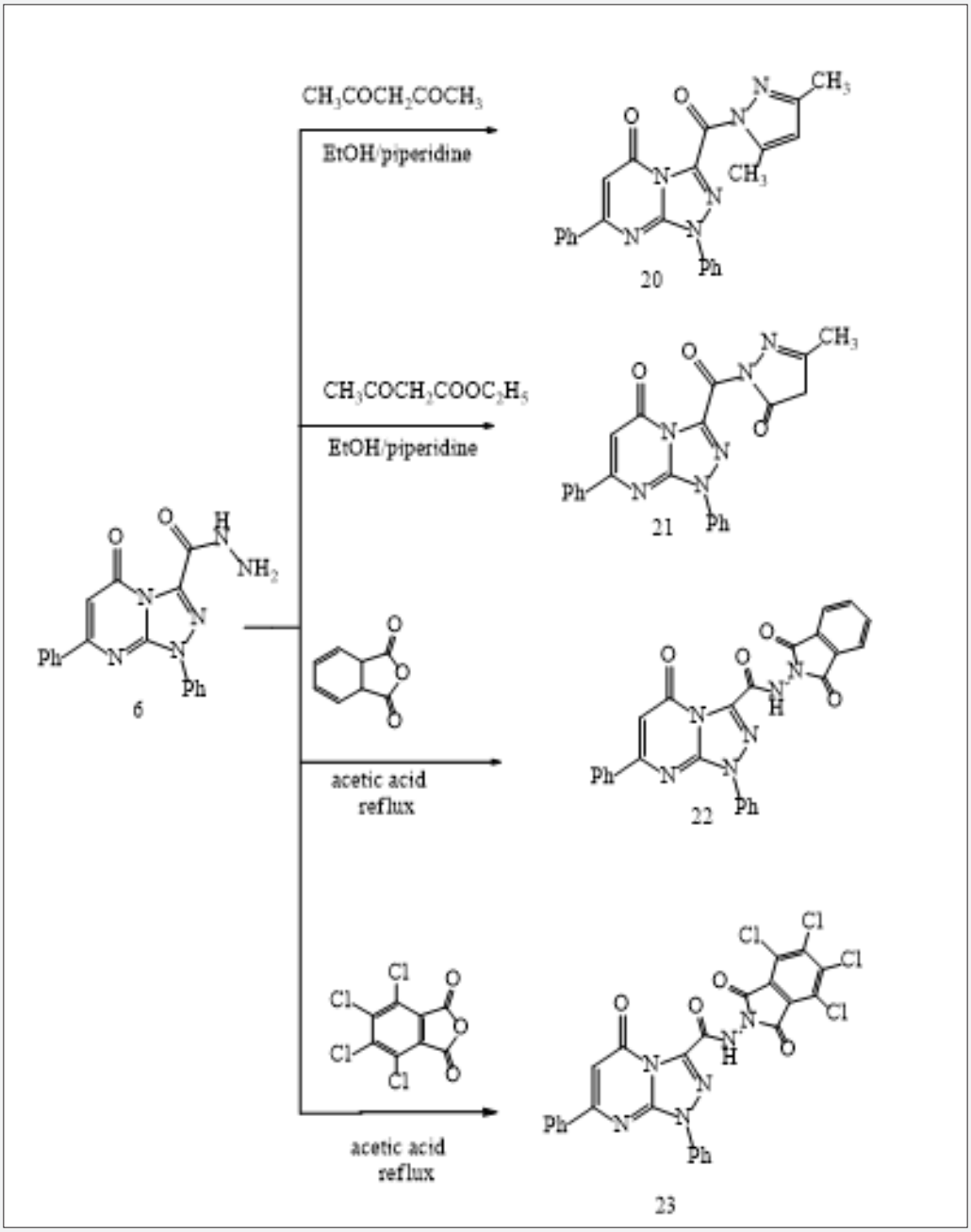

Figure 5:

Conclusion

In this mini-review, we report on the efficient procedures for the synthesis of pyrimidinedione and pyrimidinethione derivatives. The experimental results showed that the prepared product displayed outstanding pharmacological activities when screened *In-vitro* against gram positive and gram-negative strains and could be further exploited in medicinal chemistry.

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