Chapter

Construction of Biologically Active Five- and Six-Membered Fused Ring Pyrimidine Derivatives from 1,3-Diarylthiobarbituric Acids (DTBA)

Warjeet S. Laitonjam and Nimalini Moirangthem

Abstract

Several derivatives of fused pyrimidines were synthesized in maximum yields by using the respective condensation products, namely, 5-ethoxymethylene-1, 3-diaryl-2-thiobarbituric acids and 5-phenyl-methylene-1,3-diaryl-2-thiobarbituric acids, which can be obtained from 1,3-diarylthiobarbituric acids (DTBA). These condensation products possessing three electrophilic centres could undergo cyclo-condensation with various binucleophiles to give various fused heterocycles of pyrimidine derivatives, such as pyrazolo[3,4-*d*]pyrimidine-6-thiones, 5,7-diaryl-4-oxo-isoxazolo[5,4-*d*]pyrimidine-6-thiones, 5-oxo-pyrimido[4,5-*d*]pyrimidine-7-thiones, 2-thioxo-pyrano[2,3-d]pyrimidine-4-ones, pyrido[2,3-*d*]pyrimidines, quinazoline-4-oxo-2-thiones.

Keywords: diarylthiobarbituric acids, pyrazolopyrimidines, isoxazolopyrimidines, pyrimidopyrimidines, pyranopyrimidines, quinazolines

1. Introduction

The development of physiologically highly potent fused pyrimidines is a challenging task for synthetic organic chemists [1]. It is well known that pyrimidines either in isolated or in fused state are associated with a number of biological activities [2–6]. Moreover the pyrimidine nucleus containing thiouriedo linkage (-NH-C(S)-NH-) is pharmaceutically important as the development of medicine mainly arose from the heterocyclic compounds containing nitrogen and sulphur atoms [7–9]. Due to a wide range of biological activities exhibited by pyrimidine derivatives, these compounds occupy a unique place in the field of biological and medicinal chemistry. In view of such wide applications, several derivatives of fused pyrimidines were synthesized in maximum yields by using 1,3-diarylthiobarbituric acids, **1** (DTBA) which can be prepared in one pot reaction by treating 1,3-diarylthioureas with malonic acid in presence of acetyl chloride [10]. They are generally stable at room temperature and can be stored indefinitely without apparent

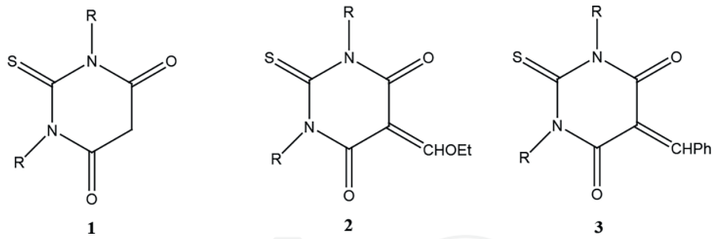
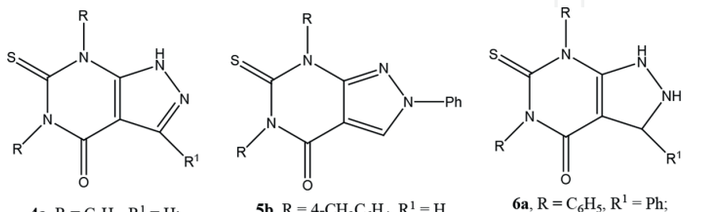


Figure 1.
Thiobarbituric acid derivatives.

decomposition. Having an active methylene group, they can furnish several condensation products for easy cyclization to give various fused heterocyclic compounds of interest. When DTBA was reacted with ethyl orthoformate and benzaldehyde to the condensation products, namely, 5-ethoxymethylene-1,3-diaryl-2-thiobarbituric acids (**2**) and 5-phenyl-methylene-1,3-diaryl-2-thiobarbituric acids (**3**), respectively were formed (**Figure 1**) [11]. As **2** and **3** possess three electrophilic centres, they could undergo cyclocondensation with various binucleophiles to give various fused heterocycles of pyrimidine derivatives [12].

2. Pyrazolo-pyrimidines

The methods reported for the synthesis of pyrazolo-pyrimidines involved a number of steps and yields were poor [13–18]. A convenient route for the synthesis of pyrazolo-pyrimidines was described [11, 19]. The condensation products, **2** and **3** have been utilized as three carbon fragments for the synthesis of 4-oxo-pyrazolo[3,4-*d*]pyriimidines, **4** and **6**, respectively. When **2** was treated with hydrazine hydrate in the presence of ethanol and acetic acid, the corresponding pyrazolo[3,4-*d*]pyrimidin-6-thione (**4**) was yielded in 65–82% overall yields (**Figure 2**). Similarly, when **2b** was treated with phenyl hydrazine in ethanol and acetic acid, 2-phenyl-5,7-bis(2′-methylphenyl)-4-oxo-pyrazolo[3,4-*d*]pyrimidin-6-thione (**5b**) was produced in 55% yield. However, when **3** was refluxed with hydrazine hydrate in ethanol and acetic acid, the corresponding (3*H*)-3-phenyl-5,7-diaryl-4-oxo-pyrazolo[3,4-*d*]pyrimidin-6-thiones (**6**) were obtained in 60–75% overall yields (**Figure 2**). It was observed that **6** could be oxidized to give the respective 3-oxo-pyrazolo-[3,4-*d*]pyrimidin-6-thiones (**7**) [11, 12, 19].



4a, R = C_6H_5, R^1 = H;
4b, R = 4-$CH_3C_6H_4$, R^1 = H;
4c, R = 4-ClC_6H_4, R^1 = H;
7a, R = C_6H_5, R^1 = Ph;
7b, R = 4-$CH_3C_6H_4$, R^1 = Ph;
7c, R = 4-ClC_6H_4, R^1 = Ph

5b, R = 4-$CH_3C_6H_4$, R^1 = H

6a, R = C_6H_5, R^1 = Ph;
6b, R = 4-$CH_3C_6H_4$, R^1 = Ph;
6c, R = 4-ClC_6H_4, R^1 = Ph

Figure 2.
Pyrazolo-pyrimidines.

It is well known that the fused heterocycles possessing the pyrazolo[3,4-*d*]pyrimidine nucleus serve as a class of compounds which exhibited a remarkable variety of biological activities [20–23]. The pyrazolo[3,4-*d*]pyrimidine compounds have been found to show similar characteristics to purines, since they are isomeric structural purine analogues, which have resulted in several potent antagonists in biological systems [24, 25].

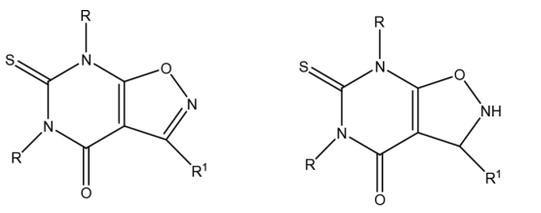
3. Isoxazolo-pyrimidines

Most of the methods for the preparation of the isoxazolo[5,4-*d*]pyrimidine system are initiated from the construction of an isoxazole ring first and followed by pyrimidine ring closure [26, 27]. DTBAs were also used as precursors for the synthesis of various isoxazolo[5,4-*d*]pyrimidines [28]. When **2** and **3** were treated with hydroxylamine hydrochloride in dehydrated alcohol and acetic acid gave 5,7-diaryl-4-oxo-isoxazolo[5,4-*d*]pyrimidin-6-thiones **(8)** in 65–85% overall yields and 3,5,7-triaryl-2,3-dihydro-4-oxo-isoxazolo[5,4-*d*]pyrimidin-6-thones (**9**) in 60–70% overall yields, respectively (**Figure 3**) [28].

It was reported that the isoxazolo-pyrimidine derivatives exhibited antifungal, antibacterial and many other important biological properties [29–31]. The biological activities in terms of the antifungal and antibacterial properties of the compounds (**8** and **9**) were determined by the standard disc diffusion method. The bacteria (*Escherichia coli* and *Bacillus subtilis*) and fungi (*Penicillium* species, *Aspergillus* sp., *Fusarium* sp. and *Trichoderma* sp) were grown in nutrient agar and potato dextrose agar (PDA) plates, respectively. Compound **9c** was found to have the highest activity against coli form organisms whereas other compounds were moderated and have less activity. The studied compounds were found to be inactive against some species of fungi, except **8b** was found to have antibiotic property in *penicillium* species.

4. Furo-pyrimidines

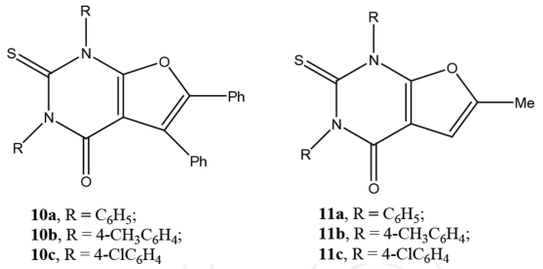
It was reported [32] that furo[2,3-*d*]pyrimidines **10** were prepared by condensing 1,3-diarylthiobarbituric acids (**1**) with benzoin in presence of *p*-toluene sulphonic acid. In another reaction, derivatives of furo[2,3-*d*]pyrimidines **11** were prepared by direct condensation of the corresponding 1,3-diarythiobarbituric acids, **1** with chloroacetone in presence of triethylamine (**Figure 4**).



8a, R = C_6H_5, R^1 = H;
8b, R = 4-$CH_3C_6H_4$, R^1 = H;
8c, R = 4-ClC_6H_4, R^1 = H

9a, R = C_6H_5, R^1 = Ph;
9b, R = 4-$CH_3C_6H_4$, R^1 = Ph;
9c, R = 4-ClC_6H_4, R^1 = Ph

Figure 3.
Isoxazolo-pyrimidines.



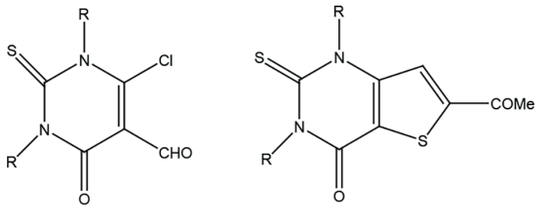
10a, R = C_6H_5;
10b, R = 4-$CH_3C_6H_4$;
10c, R = 4-ClC_6H_4

11a, R = C_6H_5;
11b, R = 4-$CH_3C_6H_4$;
11c, R = 4-ClC_6H_4

Figure 4.
Furo-pyrimidines.

5. Thieno-pyrimidines

The synthesis of thieno[2,3-*d*] pyrimidines **13** which are found to be associated with varied biological and pharmacological activities, on condensation of **12** with mesityl thioglycolate was reported (**Figure 5**) [33].



12a, R = C_6H_5;
12b, R = 4-$CH_3C_6H_4$;
12c, R = 4-ClC_6H_4

13a, R = C_6H_5;
13b, R = 4-$CH_3C_6H_4$;
13c, R = 4-ClC_6H_4

Figure 5.
Thieno-pyrimidines.

6. Pyrimido-pyrimidines

In view of the various physiological properties, the pyrimido[4,5-*d*]pyrimidines were generally prepared from derivatives of enamines [34, 35]. Various substituted 2-amino-6,8-diaryl-5-oxo-pyrimido[4,5-*d*]pyrimidin-7-thiones (**14**) in 62–75% overall yields can be synthesized by reacting the respective compounds **2** with guanidine nitrate in the presence of sodium methoxide and methanol (**Figure 6**) [36]. Similarly, the condensation products **3** were reacted with guanidine nitrate in sodium methoxide and methanol affording the corresponding substituted 3,4-dihydro-5-oxo-pyrimido[4,5-*d*] pyrimidine-7-thiones, **15** in good yields (**Figure 6**) [36].

The derivatives of pyrimido-pyrimidines are quite effective in the inhibition of cancer cell sickness [37], exhibition of diuretic activities and anti-inflammatory activities [38]. The antifungal activity for the compounds **14** and **15** was screened against *Aspergillus niger* at different concentrations by agar growth paper disc method using Czapeck's nutrient medium and DMF was used as control. The average percentage inhibition after 96 hr. was determined and the results were compared with those obtained using commercial fungicide Carbendazim. Most of the compounds were found to be fairly active at the concentrations of 1000 ppm comparable with standard fungicide. It is noteworthy that introduction of pyrimido moiety in the pyrimidine nucleus enhances the fungitoxicity to some extent and furthermore,

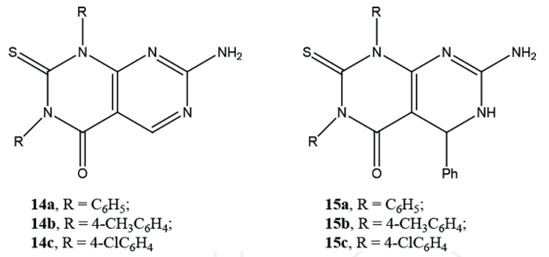


Figure 6.
Pyrimido-pyrimidines.

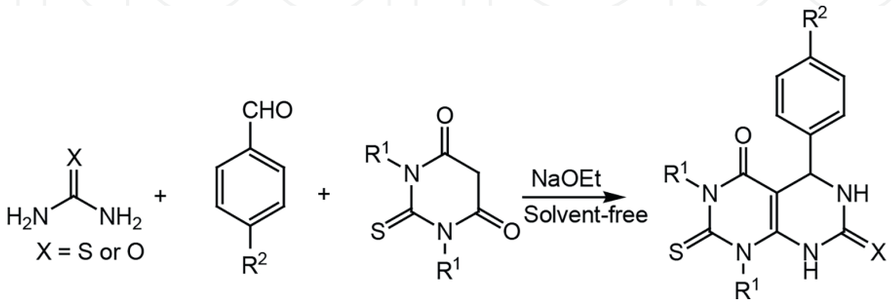


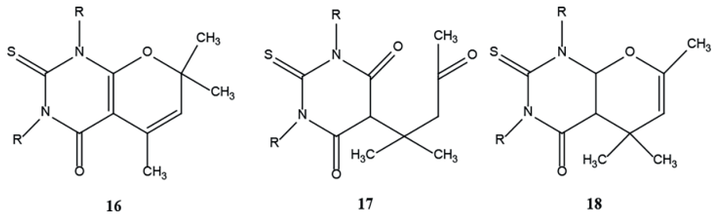
Figure 7.
Synthesis of thioxo pyrimido[4,5-d]pyrimidinone derivatives.

chloro-substituted heterocycles (**14c** and **15c**) were more active than methyl-substituted compounds (**14b** and **15b**).

Many of the earlier methods reported for the syntheses of pyrimido[4,5-*d*]pyrimidine derivatives require toxic chemicals, long reaction times, afford low to moderate yields and require many steps. A simple one-pot method for the synthesis of thioxo pyrimido[4,5-*d*]pyrimidinone derivatives by treatment of *N*,*N*-diethylthiobarbituric acids, benzaldehydes and thiourea/urea with NaOEt as the catalyst under solvent-free conditions was reported (**Scheme 1**). Several 5-aryl-2,7-dithioxo-pyrimido[4,5-d] pyrimidine-4-ones; 4-aryl-7-thioxo-pyrimido[4,5-d]pyrimidine-2,5-diones were synthesized using an eco-friendly and efficient, multi-component reaction (MCR) under solvent free conditions. The reactions proceed *via* Biginelli type condensation of aromatic aldehyde, thiobarbituric acid and urea or thiourea in presence of catalytic amount of NaOEt. The synthesized compounds were screened for anti-inflammatory activity. It was observed that the compounds containing fluoro-substituents gave good yields and showed high anti-inflammatory activities. There are no reports available on the formation of Biginelli products using NaOEt as a catalyst under solvent-free conditions (**Figure** 7).

7. Pyrano-pyrimidines

Pyrano[2,3-*d*]pyrimidine derivatives could be synthesized *via* a multicomponent domini Knoevenagel/hetero Diels-Alder reaction of 1,3-dimethyl barbituric acid with an aromatic aldehyde and ethyl vinyl ether or 2,3-dihydrofuran in presence of 1 mol % of indium (III) chloride. The reaction also proceeds in aqueous media without using any catalyst, but the yield is comparatively less (65–75%). Preparation of naturally occurring complex molecules containing a uracil ring possesses significant synthetic challenges. The development of clinically useful anticancer (5-fluorouracil)



16 **17** **18**

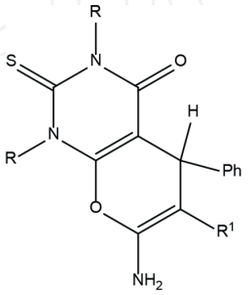
Figure 8.
Pyrano-pyrimidines.

and antiviral drugs (AZT, DDC, DDI, BVDV) has renewed interest in the synthetic manipulation of uracils.

Ahluwalia *et al*. [39] reported the synthesis of pyrano[2,3-*d*] pyrimidines **16** by reacting thiobarbturic acids, **1** with mesityl oxide in the presence of pyridine (**Figure 8**). The products were identical with the products obtained by the reaction of appropriate thiobarbituric acids with acetone in presence of triethylamine. The reaction of thiobarbituric acids with mesityl oxide in the absence of any base gave the corresponding open chain compounds **17** which on heating with glacial acetic acids and phosphorus pentoxide gave the corresponding cyclic compounds **18** [39].

Although a variety of routes for the synthesis of these compounds have been appeared in the literature, the majority of them involve a number of steps, drastic conditions, long reaction time and low yields [40–44]. Moreover, very few methods are reported for the synthesis of 2-thioxo-pyrano[2,3-d]pyrimidine-4-ones, as most of the methods reported are of pyrano[2,3-*d*]pyrimidines. In search of an efficient method and in continuation to our studies on fused pyrimidine derivatives, we report the full details of the work and studies related to the synthesis of 7-amino-1,3-diaryl-5-phenyl-2-thioxo-pyrano[2,3-d]pyrimidin-4(1*H*)-ones (**19**) from DTBA by reacting with various arylidenes, such as, phenylmethylenemalononitrile, ethyl phenylmethylene-cyanoacetate and phenylmethylenecyanoacetamide in presence of sodium methoxide and methanol [45]. Thus, the reaction of DTBA with arylidenes and sodium methoxide in presence of methanol by refluxing for 6 hr. afforded the compounds **19** in 70–82% overall yields (**Figure 9**).

Compounds containing dihydro-5H-pyrano[2,3-*d*]pyrimidines moiety have interesting biological properties [46]. In addition, compounds having a chalcone



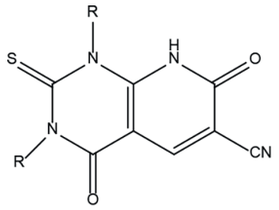
19a, R = C_6H_5, R_1 = CN;
19b, R = 4-ClC_6H_4, R_1 = CN;
19c, R = 4-$CH_3C_6H_4$, R_1 = CN;
19d, R = 2-$CH_3C_6H_4$, R_1 = CN;
19e, R = 4-ClC_6H_4, R_1 = OH;
19f, R = 4-$CH_3C_6H_4$, R_1 = OH

Figure 9.
2-Thioxo-pyrano[2,3-d]pyrimidine-4-ones.

unit attached to the pyranopyrimidine ring are efficient herbicides [47]. The antifungal screening of the synthesized compounds (**19**) were done *in vitro* at 100 and 300 μg/ml solution against the two types of fungi, namely, *Fusarium oxysporum* and *Helminthosporium oryzae* using acetone as solvent. The zones of inhibition were measured in mm. The result showed that most of the compounds exhibit moderate to high activity against both fungi. Incorporation of chlorine increased the activity of high order [48]. The synthesized compounds, **19** were also screened against gram negative bacteria *Escherichia coli* (MTCC 739) and gram positive bacterium *Bacillus subtilis* (MTCC 121). The agar cup-plate method was used and nutrient agar was culture medium for the antibacterial activity. The solvent acetone served as a control. The zone of inhibition frame was measured in mm. The result of antibacterial activity showed that compounds **19b** and **19e** showed the most active compound against *B. subtilis* only, while **19a** and **19c** do not show any zone of inhibition against these bacteria [48].

8. Pyrido-pyrimidines

Very few substituted pyrido[2,3-*d*]pyrimidines were synthesized from 6-aminouracils [49, 50]. The synthesis of substituted 3-cyano-6,8-diaryl-2,5-dioxo-pyrido[2,3-*d*]pyrimidin-7-thiones (**20**) from the corresponding condensation product (**2**) derived from 1,3-diarythiobarbituric acids were also reported [12]. Thus, the reaction of **2** with cyanoacetamide in presence of sodium isopropoxide and isopropanol afforded the corresponding pyrido[2,3-*d*]pyrimidines (**20**) in 62–74% overall yields (**Figure 10**).



20a, R = C_6H_5;
20b, R = 4-$CH_3C_6H_4$;
20c, R = 4-ClC_6H_4

Figure 10.
Pyrido-pyrimidines.

9. Quinazolines

Quinazolines are interesting targets for new method development due to their importance in a broad range of therapeutic areas [51, 52]. Quinazoline derivatives, which possess a wide range of biological activities contain the 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine structural moiety in their heterocyclic rings [53–58].

The synthetic methods available for the preparation of quinazolines involved the amidation of 2-aminobenzoic acid or its derivatives, i.e. 2-aminobenzonitrile, 2-aminobenzoate, and 2-arylnitrilium salts, followed by oxidative ring closure [59–63]. Other synthetic pathways include the cyclization of anthranilamides with aldehydes [64], and with ketones or acid chlorides under acidic or basic conditions [65–67]. These methods involved multistep processes, poor yields, toxic reagents and

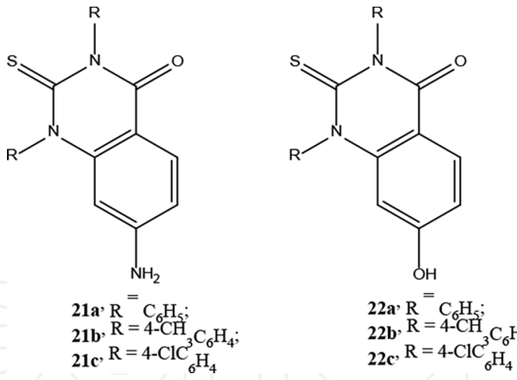


Figure 11.
Quinazolines.

time-consuming experimental procedures. Moreover, very few methods are reported for the synthesis of 2-thioxoquinazoline-4-ones, as most of the methods reported are of quinazoline-2,4(1*H*,3*H*)-diones, from various sources [61, 62, 68–75].

Recently, Saeed *et al*. [76] reported the base catalysed intramolecular nucleophilic cyclization of substituted thioureas in the presence of DMF to afford the 2-thioxoquinazoline-4-ones. The solid-phase synthesis for the preparation of2-thioxoquinazoline-4-one had been reported [77–80]. Treatment of 5-ethoxymethylene-1,3-diaryl-2-thiobarbituric acids (**2**) with malononitrile in presence of NH_4OAc and acetic acid with $ZnCl_2$ as catalyst in refluxing condition gave the corresponding 2-thioxoquinazolin-4-ones, **21** in 78–85% overall yields [81] (**Figure 11**). However, the reaction of **2** with ethyl cyanoacetate in presence of ammonium acetate and acetic acid with $ZnCl_2$ as a catalyst gave 7-hydroxy-2,3-dihydro-2-thioxo-1,3-diarylquinazolin-4(*1H*)-ones, **22** in 76–87% overall yields [81].

The synthesized compounds **21** and **22** were screened *in vitro* for their antimicrobial activities [82, 83]. Cytotoxicity studies were performed for the compounds on human lung cancer cell line A549 using an MTT assay. The A549 cells were grown at 37°C, 5% CO_2 and 100% relative humidity.

10. Benzo[5,6]chromeno[2,3-d]pyrimidines

Novel 2-thioxo-benzo[5,6]chromeno[2,3-d]pyrimidin-4-one derivatives were synthesized in aqueous media using cetylpyridinium chloride (CPC) as micellar catalyst in three-component one-pot reaction involving thiobarbituric acids, aromatic aldehydes and β-napthol [84]. The synthesized compounds were found to show antioxidant and cytotoxic activities (**Figure 12**).

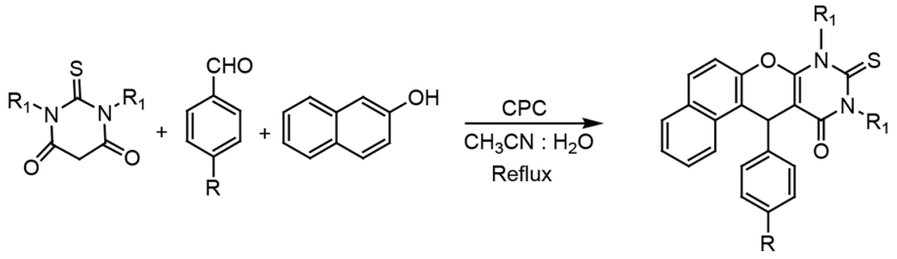


Figure 12.
Synthesis of 2-thioxo-benzo[5,6]chromeno[2,3-d]pyrimidin-4-one derivatives.

11. Pyrazolopyrano-pyrimidinones

Tricyclic fused pyrazolopyranopyrimidines were synthesized by one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and barbituric acid in good to excellent yields (88–95%) [85]. Another method for the synthesis of pyrazolopyranopyrimidines was employed using DABCO as catalyst in water [86].

A new series of triheterocyclic compounds containing pyrazole, pyran, and pyrimidinone rings was synthesized via a one-pot condensation of ethylacetoacetate, hydrazine hydrate, barbituric acid, and aromatic aldehydes in the presence of catalytic amounts of titanium dioxide nanowires [87]. Various functional groups were well tolerated under the optimized reaction conditions. A highly efficient, green protocol, one-pot four-component reaction involving thiobarbituric acid, hydrazine hydrate, ethyl acetoacetate and aromatic aldehydes for the synthesis of 7-thioxo-pyrazolopyrano-pyrimidinone derivatives has been accomplished using SDS (sodium dodecyl sulphate) as a catalyst (**Figure 13**) [88]. The procedure offers the advantages of green solvent, easy work-up avoiding the chromatographic separation and use of inexpensive, biodegradable, reusable catalyst. These novel 7-thioxo-pyrazolopyrano-pyrimidinone derivatives were screened for antimicrobial, and antioxidant activities. It was found that 3-methyl-4-(2,4-dichlorophenyl)-6,8-diethyl-7-thioxo4,6,7,8-tetrahydropyrazolo[4′,3′:5,6]pyrano-[2,3-d]pyrimidin-5(1H)-one has shown high antifungal and anti-bacterial activities against the tested fungi and bacteria, which may be due to the presence of chlorine atoms [88]. All the prepared pyrazolopyranopyrimidines were tested as anti-inflammatory agents and some of them revealed moderate to potent anti-inflammatory activity [89].

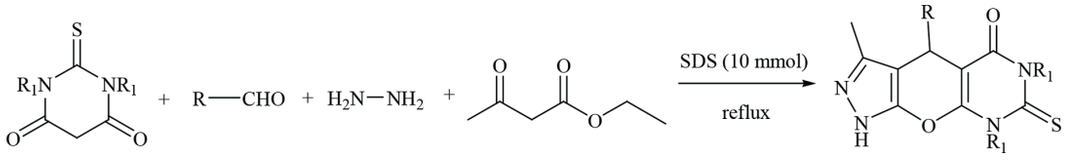


Figure 13.
Synthesis of 7-thioxo-pyrazolopyrano-pyrimidinone derivatives.

12. Benzo[4,5]thiazolopyrimido[5,4-d]pyrimidines

Medhabati *et al*. [90] reported the synthesis of 2-thio-5-arylbenzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one derivatives under aqueous medium. Benzo[4,5]thiazolopyrimido[5,4-d]pyrimidines were synthesized by condensation

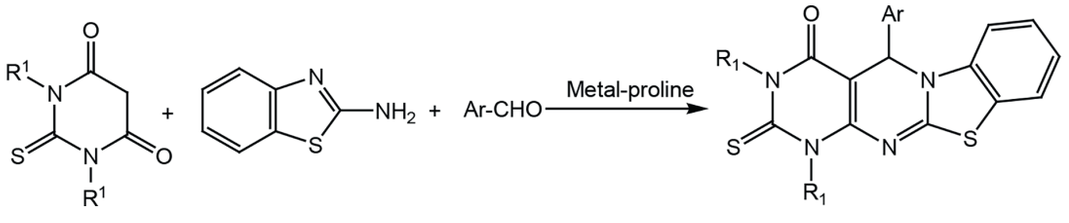


Figure 14.
Synthesis of 2-thio-5-arylbenzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones.

of thiobarbituric acids, 2-aminobenzothiazole and aldehydes using metal-proline as catalyst (**Figure 14**).

13. Pyrimido[5,4-e[1,3,4]thiadiazolo[3,2-a]pyrimidines

An efficient one-pot method for the synthesis of 2-methyl-5,7,9-triphenyl-8-thioxo-8,9-dihydro-5H-pyrimido[5,4-e[1,3,4]thiadiazolo[3,2-a] pyrimidin-6(7H)-one and its derivatives was reported. The present protocol is also extendable to a wide variety of substrates. The advantages of this protocol are the use of easily available catalyst, short reaction time, easy work-up, ease of product isolation, and high yield (**Figure 15**).

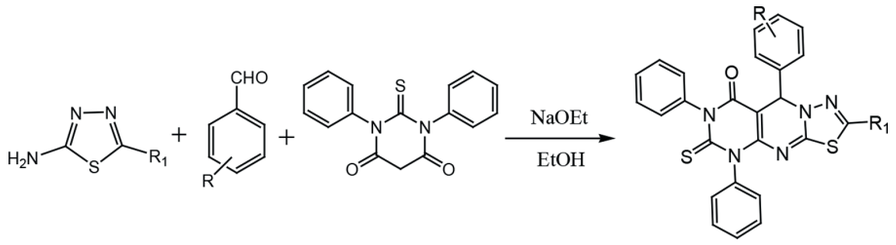


Figure 15.
Synthesis of Pyrimido[5,4-e[1,3,4]thiadiazolo[3,2-a]pyrimidines.

14. Conclusion

Many fused pyrimidine derivatives are belonged to the most important heterocyclic systems, and there are numerous synthetic preparative methods for these compounds. However, in some cases, difficult access to key intermediates, or to their precursors, was a serious limitation for the above syntheses. Various fused pyrimidines were synthesized in maximum yields by using the respective condensation products, namely, 5-ethoxymethylene-1,3-diaryl-2-thiobarbituric acids and 5-phenyl-methylene-1,3-diaryl-2-thiobarbituric acids, which can be obtained from 1,3-diarylthiobarbituric acids (DTBA). These condensation products possessing three electrophilic centres could undergo cyclocondensation with various binucleophiles to give various fused heterocycles of pyrimidine derivatives, such as, pyrazolo[3,4-*d*] pyrimidine-6-thiones, 5,7-diaryl-4-oxo-isoxazolo[5,4-*d*]pyrimidine-6-thiones, 5-oxo-pyrimido[4,5-*d*]pyrimidine-7-thiones, 2-thioxo-pyrano[2,3-d]pyrimidine-4-ones, pyrido[2,3-*d*]pyrimidines, quinazoline-4-oxo-2-thiones, etc.

DOI: http://dx.doi.org/10.5772/intechopen.108842

Author details

Warjeet S. Laitonjam[1*] and Nimalini Moirangthem[2]

1 Department of Chemistry, Manipur University, Imphal, Manipur, India

2 ARS Dharma College, University of Delhi, New Delhi, India

*Address all correspondence to: warjeet@yahoo.com

References

[1] Katritzky AR, Rees CW. Comprehensive Heterocyclic Chemistry. New York: Pergamon Press; 1984. p. 173

[2] Moriguchi I, Kaneniwa N. Spectroscopic studies on molecular interactions. IV. Charge-transfer properties and antibacterial activity of sulfonamides. Chemical Pharmaceutical Bulletin. 1969;**17**(12):2554-2557

[3] Arakawa K, Miyasaka T, Ochi H. Heterocyclic compounds. II. Acetyl transfer reactions of 3-acetoxy-1-acetyl-5-methylpyrazole and related compounds. Chemical and Pharmaceutical Bulletin. 1974;**22**:214-223

[4] Ahluwalia VK, Das U. A facile entry to pyrimidine-derivatives - synthesis of 5-(1,3-dithiolan dithian-2-ylidene) and pyrano[2,3-d]pyrimidines. Industrial Journal of Chemistry. 1996;**35B**:673-676

[5] Zeid IF, Abdel-Rahman AAH, Abdel-Megeid AES, El-Etrawy ASH. Synthesis of new thiolated acyclonucleosides with potential anti HBV activity. Nucleosides, Nucleotides. 1995;**18**:95-111

[6] Sengupta AK, Agarwal KC, Mushtaq M. Synthesis and anticonvulsant activity of some substituted Thiosemicarbazides and triazoles. Industrial Journal of Chemistry. 1979;**17B**:184-185

[7] Singh H, Yadav LDS. Synthesis of some 5-Aryl-2-heteroaryl/heteroarylamino-1, 3, 4-oxadiazoles as potential fungicides. Agricultural Biological Chemistry. 1976;**40**:759-764

[8] Rashad AE, Heikal OA, El-Nezhawy AOH, Abdel-Megeid FME. Synthesis and isomerization of thienotriazolopyrimidine and thienotetrazolopyrimidine derivatives with potential anti-inflammatory activity. Heteroatom Chemistry. 2005;**16**:226-234

[9] Shukla HK, Desai NC, Astik RR, Thaker KA. Studies on some thiosemicarbazones and 1, 3, 4-thiadiazoles as potential antitubercular and antibacterial agents. Journal of Industrial Chemical Society. 1984;**61**:168-171

[10] Das IND, Dutt S. Colour in relation to chemical constitution of the organic and inorganic salts of Jsonitroso-diphenyl-thio-barbituric acid and its higher homologues and analogues. Proceedings of the Indian Academy Science. 1938;**8A**:145-159

[11] Laitonjam WS, Nongmeikapam AD. Synthesis of substituted 4-oxopyrazole[3,4-d]pyrimidine-6-thiones from 1,3-diaryl-5-ethoxymethylene-2-thiobarbituric acids. Indian Journal of Chemistry. 1994;**33B**:1091-1092

[12] Laitonjam WS, Thokchom HS, Nongmeikapam AD. Synthesis of fused pyrazolo-, isoxazolo-, pyrimido- and pyridopyrimidines. Canadian Journal of Chemistry. 2005;**83**:1056-1062

[13] Kohra S, Tomonaga Y, Hosomi A. Synthesis of pyrimidine derivatives by the reaction of ketene dithioacetals with amides. Journal of Heterocycling Chemistry. 1988;**25**:959-968

[14] Swelam SA, Abd El-Salam OS, Zaki MEA. Synthesis of some pyrazolo[3,4-d]pyrimidines and their fused triazole and tetrazole derivatives. Journal of the Serbian Chemical Society. 1999;**64**:655-662

[15] Mect SM, Werner D. A concise synthesis of substituted 4-alkylaminopyrazolo[3,4-d] pyrimidines. Journal of the Chemical Society, Perkin Transactions. 1973;**1**:1903-1906

[16] Papesch V, Dodson RM. Isomeric Pyrazolo[4,3-d]pyrimidinediones. The Journal of Organic Chemistry. 1965;**30**:199-203

[17] Maki Y, Izuta K, Suzuki M. A new synthesis of pyrazolo[3,4-d]pyrimidines. Journal of Chemical Society. 1971;**1971**:1442-1443

[18] Yoneda F, Nagamatsu T, Nagamura T. Synthesis of pyrazolo[3,4-d]pyrimidines by intramolecular cycloaddition of azahexatrienes. Journal of the Chemical Society, Perkin Transactions. 1977;**1**:765-767

[19] Laitonjam WS, Nongmeikapam AD. A facile synthesis of 2(3H)-3,5,7-triphenyl-2(3H)-3-phenyl-5,7-bis(substituted phenyl)-4-oxo-pyrazolo[3,4-d]pyrimidine-6-thiones. Indian Journal of Heterocycling Chemistry. 1995;**5**:139-140

[20] Robins RKP, Purine Antagonists I. Synthesis of some 4,6-substituted pyrazolo [3,4-d] pyrimidines[1]. Journal of the American Chemical Society. 1956;**78**:784-790

[21] White FR. 4-Aminopyrazolo9(3,4-d) pyrimidine and three derivatives. Cancer Chemotherapy Reports. 1959;**3**:26-36

[22] Jun Scott JL, Foye LV. Clinical evaluation of 4-propylamino-1-H-pyrazolo (3,4-d) pyrimidine. Cancer Chemotherapy Reports. 1962;**20**:73-80

[23] Robins RK. Antitumor activity and structural relationships of Purine derivatives and related compounds against neoplasms in experimental animals. Journal of Medicinal Chemistry. 1964;**7**:186-199

[24] Kobayashi S. The synthesis and xanthine oxidase inhibitory activity of pyrazolo[3, 4-d]pyrimidines. Chemical Pharmaceutical Bulletin Japan. 1973;**21**:941-951

[25] Marr JJ, Berens RL, Nelson DJ, Lafon SW. Antileishmanial effect of allopurinol and allopurinol ribonucleoside on intracellular forms of *Leishmania donovani*. Biochemical Pharmacology. 1980;**29**:2397-2398

[26] Taylor EC, Garcia EE. The synthesis of 4-Aminoisoxazolo[5,4-d]pyrimidines[1]. The Journal of Organic Chemistry. 1964;**29**:2116-2120

[27] Rajagopalan P, Talaty CN. Synthesis of 4-hydroxy-, 4-chloro-, 4-amino- and 4-substituted aminoisoxazolo [5.4-d] pyrimidines. Tetrahedron. 1967;**23**:3541-3543

[28] Laitonjam WS, Nongmeikapam AD. Synthesis of substituted 4-oxo and substituted 2,3-dihydro-4-oxoisoxazolo[5,4-d]pyrimidin-6-thiones. Indian Journal of Chemistry. 1996;**35B**:478-479

[29] Kaim L, Grimaud L, Patil P. Three-component strategy toward 5-membered heterocycles from isocyanide dibromides. Organic Letters. 2011;**13**:1261-1263

[30] Tu S-J, Zhang XH, Han Z-G, Cao XD, Wu S-S, Yan S, et al. Synthesis of isoxazolo[5,4-b]pyridines by microwave-assisted multi-component reactions in water. Journal of Combinatorial Chemistry. 2009;**11**:428-432

[31] Bellary JM, Badiger VV. Synthesis of some Isoxazolo[4,5-e]-s-triazolo[4,3-c] pyrimidines. Indian Journal of Chemistry. 1981;**20B**:654

[32] Kaur M. Ph.D. Thesis, Delhi University, 1989.

[33] Ahluwalia VK, Dahiya A, Bala M. Novel synthesis of thieno[2,3-c]pyrazoles and thieno[2,3-d]pyrimidines. Indian Journal of Chemistry. 1996;**35B**:715

[34] Taminaga Y, Okuda H, Matsuda Y. Synthesis of Pyrimido[4,5-d] pyrimidines. Heterocycles. 1979;**12**:503-504

[35] Jiang B, Shi F, Tu S-J. Microwave-assisted multicomponent reactions in the heterocyclic chemistry. Current Organic Chemistry. 2010;**14**:357-378

[36] Laitonjam WS, Nongmeikapam AD. Synthesis of pyrimido[4,5-d]pyrimidines as antifungal agents. Indian Journal of Heterocycling Chemistry. 1998;**7**:193-196

[37] Kruithof A, Ruijter E, Orru RVA. Microwave-assisted multicomponent synthesis of heterocycles. Current Organic Chemistry. 2011;**15**:204-236

[38] Hirota K, Huang J, Sajiki H, Maki Y. Pyrimidines. Part 57. A Versatile Synthesis of Pyrimido[4,5-d]pyrimidine-2,4,5-trione Derivatives. Heterocycles. 1986;**24**:2293

[39] Ahluwalia VK, Sharma HR, Tyagi R. A novel one step synthesis of pyrano (2,3-d) pyrimidines. Tetrahedron. 1986;**42**:4045-4048

[40] Ahmed MG, Romman UKR, Ahmed SM, Akhter K, Halim ME, Salauddin M. A study on the synthesis of 5,7-diaryl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano[2,3-d]pyrimidines. Bangladesh Journal of Science Industrial Research. 2006;**41**(3-4):119

[41] Andotra CS, Khajuria J, Kaur S. Synthesis of 1,2,3,4-tetrahydro-2,4-dioxo-7-(2,4-dialkoxyphenyl)-5-substituted phenyl-5H-pyrano-[2,3-d]-pyrimidines and 3-(2,4-dialkoxyphenyl)-5-substituted phenylisoxazoles. Journal of Industrial Chemical Society. 2006;**83**:509-512

[42] Yu J, Wang H. Green synthesis of pyrano[2,3-d]pyrimidine derivatives in ionic liquids. Synthetic Communications. 2005;**35**:3133-3140

[43] Devi I, Bhuyan PJ. A novel microwave-assisted one-pot synthesis of Pyrano[2,3-d]pyrimidines and pyrido[2,3-d]pyrimidines via a three component reaction in solvent-free condition. Synlett. 2004:283-286

[44] Prajapati D, Gohain M. An efficient synthesis of novel pyrano[2,3-d]- and furopyrano[2,3-d]pyrimidines via indium-catalyzed multi-component domino reaction. Beilstein Journal of Organic Chemistry. 2006;**2**:1-5

[45] Laitonjam WS, Moirangthem N. A facile synthesis of 7-amino-1,3-diaryl-5-phenyl-2- thioxo-pyrano[2,3-d] pyrimidine-4(5H)-one. American Chemical Science Journal. 2011;**1**:58-70

[46] Yun M, Changtao Q, Limin W, Min Y. Convenient selective synthesis of pyrano[2,3-d]pyrimidines. Russian Chemical Bulletin. 2000;**57**:2223-2226

[47] Antonio H, Roberto MA, Pedro R, John A. An easy synthesis of pyranopyrimidines. Monatshefte fur Chem. 2006;**137**:1421-1430

[48] Moirangthem N. Ph. D. Thesis, Manipur University, Manipur, 2010.

[49] Broom AD, Shin JL, Anderson GL. Pyrido[2,3-d]pyrimidines. IV. Synthetic studies leading to various oxopyrido[2,3-d]pyrimidines. The Journal of Organic Chemistry. 1976;**41**:1095-1099

[50] Bhuyan P, Boruah RC, Sandhu JS. Studies on uracils. 10. A facile one-pot synthesis of pyrido[2,3-d]- and pyrazolo[3,4-d]pyrimidines. The Journal of Organic Chemistry. 1990;**55**:568-571

[51] Connolly DJ, Cusack D, O'Sullivian TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. Tetrahedron. 2005;**61**:10153-10202

[52] Mhaske SB, Argade NP. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. Tetrahedron. 2006;**62**:9787-9826

[53] Xia Y, Yang ZY, Hour MJ, Kuo SC, Xia P, Bastow KF, et al. Part 204: Synthesis and biological evaluation of substituted 2-aryl quinazolinones. Bioorganic & Medicinal Chemistry Letters. 2001;**11**:1193-1196

[54] De Clercq E. New developments in anti-HIV chemotherapy. Current Medicinal Chemistry. 2001;**8**:1543-1572

[55] Corbett JW. A review of recent HIV-1 non-nucleoside reverse transcriptase inhibitor research. Current Medicinal Chemistry. 2002;**1**:119-140

[56] Le Mahieu RA, Carson M, Welton AF, Baruth HW, Yaremko B. Synthesis and antiallergy activity of 5-oxo-5H-thiazolo[2,3-b]quinazolinecarboxylic acids. Journal of Medicinal Chemistry. 1983;**26**:107-110

[57] Vandenberk J, Kennis L. V. der Heertum, A. V. U.S. Patent 4, 522, 945. 1985

[58] Sohda T, Makino H, Boba A. Eur. Patent E.P. 0567107. 2001

[59] Jiarong L, Xian C, Daxin S, Shuling M, Qing L, Qi Z, et al. A new and facile synthesis of Quinazoline-2,4(1H,3H)-diones. Organic Letters. 2009;**11**:1193-1196

[60] Li Z, Huang H, Sun H, Jiang H, Liu H. Microwave-assisted efficient and convenient synthesis of 2,4(1H,3H)-Quinazolinediones and 2-Thioxoquinazolines. Journal of Combinatorial Chemistry. 2008;**10**:484-486

[61] Kornet MJ. Journal of Combinatorial Chemistry. 2008;**10**:1533

[62] Couture A, Cornet H, Grandclaudon P. An expeditious synthesis of 2-aryl- and 2-Alkylquinazolin-4(3H)-ones. Synthesis. 1991:1009-1010

[63] Kotsuki H, Sakai H, Morimoto H, Suenaga H. A new quinazoline synthesis. Synlett. 1999:1993-1995

[64] Abdel-Jalil RL, Volter W, Saeed M. A novel method for the synthesis of 4(3H)-quinazolinones. Tetrahedron Letters. 2004;**45**:3475-3476

[65] Feldman JR, Wagner EC. Some reactions of methylene-bis-amines as ammono-aldehydes. The Journal of Organic Chemistry. 1942;**7**:31-42

[66] Yale HL. Substituted 2,3-dihydro-4(1H)quinazolinones, 2. Journal of Heterocycling Chemistry. 1977;**14**:1357-1359

[67] Mhaske SB, Argade NP. Regioselective quinazolinone-directed ortho lithiation of Quinazolinoylquinoline: Practical synthesis of naturally occurring human DNA topoisomerase I poison Luotonin a and Luotonins B and E. The Journal of Organic Chemistry. 2004;**69**:4563-4566

[68] Petrov JS, Andreev GN. Synthesis of 2,4(1h,3h)-quinazolinedione and 3-substituted 2,4(1h,3h)-quinazolinediones. Organic Preparations and Procedures International. 2005;**37**:560-565

[69] Willis MC, Snell RH, Fletcher AJ, Woodward RL. Tandem palladium-catalyzed urea arylation–intramolecular Ester Amidation: Regioselective synthesis of 3-alkylated 2,4-Quinazolinediones. Organic Letters. 2006;**8**:5089-5091

[70] Taylor EC, Shvo Y. Heterocyclic synthesis from o-aminonitriles. XXX. Synthesis of some diazasteroids. The Journal of Organic Chemistry. 1968;**33**:1719-1727

[71] Papadopoulos EP. Reactions of o-aminonitriles with isocyanates. 2. A facile synthesis of imidazo[1,2-c] quinazoline-2,5-(3H,6H)dione. Journal of Heterocycling Chemistry. 1981;**18**:515-518

[72] Papadopoulos EP. Reactions of o-aminonitriles with isocyanates. 1. A two-step synthesis of 2,6-dihydroimidazo[1,2-c]quinazolin-5-(3H)one. Journal of Heterocycling Chemistry. 1980;**17**:1553-1558

[73] Mizuno T, Okamoto T, Ito T, Miyata T. Synthesis of 2,4-dihydroxyquinazolines using carbon dioxide in the presence of DBU under mild conditions. Tetrahedron Letters. 2000;**41**:1051-1053

[74] Mizuno T, Ishino Y. Highly efficient synthesis of 1H-quinazoline-2,4-diones using carbon dioxide in the presence of catalytic amount of DBU. Tetrahedron. 2002;**58**:3155-3158

[75] Mizuno T, Iwai T, Ishino Y. The simple solvent-free synthesis of 1H-quinazoline-2,4-diones using supercritical carbon dioxide and catalytic amount of base. Tetrahedron Letters. 2004;**45**:7073-7075

[76] Saeed A, Shaheen U, Bolte M. Synthesis, characterization and crystal structure of some novel 1-Aryl-2-Thioxo-2,3-dihydro-1H-Quinazolin-4-ones. Journal of Chinese Chemical Society. 2010;**57**:82-88

[77] Makino S, Suzuki N, Nakanishi E, Tsuji T. Efficient solid-phase synthesis of quinazoline-2-thioxo-4-ones with SynPhase™ lanterns. Tetrahedron Letters. 2000;**41**:8333-8337

[78] Makino S, Nakanishi E, Tsuji T. Solid-phase synthesis of 1,3-disubstituted 2-thioxoquinazoline-4-ones using S_NAr reaction. Tetrahedron Letters. 2001;**42**:1749-1752

[79] Makino S, Nakanishi E, Tsuji T. Solid-phase synthesis, combinatorial chemistry, Heterocyle, SNAr, 2,1,3-Benzothiadiazin-4-one 2-oxide. Bulletin of the Korean Chemical Society. 2003;**24**:389-392

[80] Ivachtchenko AV, Kovalenko SM, Drushlyak OG. Synthesis of substituted 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines and 4-Oxo-3,4-dihydroquinazoline-2-thioles. Journal of Combinatorial Chemistry. 2003;**5**:775-788

[81] Laitonjam WS, Moirangthem N. A new and facile synthetic approach to substituted 2-thioxoquinazolin-4-ones by the annulation of a pyrimidine derivative. Journal of Organic Chemistry. 2010;**6**:1056-1060

[82] Hewitt W, Vincent S. Theory and Application of Microbiological Assay. New York: Academic Press, Inc.; 1989

[83] Cremer A. Antibiotic Sensitivity and Assay Tests. 4th ed. London: Butterworths; 1980. p. 521

[84] Dini A, Medhabati DT, Reena H, Warjeet SL. Synthesis and screening for antioxidant and cytotoxic activities of novel 2-thioxobenzo[f]chromeno[2,3-d] pyrimidin-4-ones derived by

cetylpyridinium chloride catalyzed multicomponent reactions in aqueous micellar media. Industrial Journal of Chemistry. 2021;**60B**:1243-1257

[85] Li XT, Zhao AD, Mo LP, Zhang ZH. Meglumine catalyzed expeditious four-component domino protocol for synthesis of pyrazolopyranopyrimidines in aqueous medium. RSC Advances. 2014;**4**:51580-51588

[86] Heravi MM, Mousavizadeh F, Ghobadi N, Tajbakhsh M. A green and convenient protocol for the synthesis of novel pyrazolopyranopyrimidines via a one-pot, four-component reaction in water. Tetahedron Letters. 2014;**55**:1226-1228

[87] Dastkhoon S, Tavakoli Z, Khodabakhshi S, Baghernejad M, Abbasabadi MK. Nanocatalytic one-pot, four-component synthesis of some new triheterocyclic compounds consisting of pyrazole, pyran, and pyrimidinone rings. New Journal of Chemistry. 2015;**39**:7268-7271

[88] Dini A, Shyamkesho MS, Warjeet SL. Synthesis, antimicrobial and antioxidant activities of novel 7-thioxo4,6,7,8-tetrahydro-pyrazolo[4′,3′,5,6] pyrano[2,3-d]pyrimidin-5(1H)-ones derived by SDS catalyzed multicomponent reactions in aqueous micellar media. Natural Products Journal. 2018;**8**:1-11

[89] Zaki MEA, Soliman HA, Hiekal OA, Rashad AE. Pyrazolopyranopyrimidines as a Class of Anti-Inflammatory Agents. Tübingen: Verlag der Zeitschrift für Naturforschung; 2005

[90] Medhabati DT, Ranjana DT, Warjeet SL. Synthesis of biologically active 2-thio-5-arylbenzo[4,5] thiazolopyrimido [5,4-d]pyrimidin-4-one derivatives catalyzed by metal proline in water. Industrial Journal of Chemistry. 2021;**60B**:1230-1242