*Iranian Journal of Organic Chemistry Vol. 16, No.2 (2024) 3797-3806*

# Design: mechanism of formation and emerging applications of amino dithio acetal derivatives of pyrimidines and allied nitrogen heterocycles

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Received: February 2024; Revised: April 2024; Accepted: April 2024

**Abstract:** Nitrogen heterocycles have been frequently synthesised and play a pivotal role in synthetic organic chemistry. Pyrimidines are important member of six membered nitrogen heterocycles and have been used as model substrates in a variety of reactions. 2-cyanopyrimidine **1** is an electron deficient aryl nitrile which upon interaction with ethane 1,2-dithol under buffered aqueous conditions afforded amino dithioacetal (ADTA) **2** in excellent yields. However, 2,3-dicyano pyrazine **3** results **4** and **5** when allowed to react with ethane dithol. Pyrazinoquinoxaline is another important member of class of nitrogen heterocycles with inherent properties. A series of dicyanopyrazinoquinoxalines (DCPQs) **9-12** have been obtained when *ortho*-phenylenediamine **6** and allied compounds were interacted with pyrazine derivatives. A simple and convenient method for the synthesis of quinoxaline derivatives **17** has also been developed from cinnamils **15** in water under reflux/microwave irradiation conditions. This article concentrates on the design and suggested mechanism of different amino dithioacetals (ADTA,s) of pyrimidines, dicyanopyrazinoquinoxalines and allied nitrogen heterocycles. A wide range of emerging applications of these heteroatom compounds have also been discussed.

**Keywords:** Pyrimidines, Aryl nitrile, 1,2-Dithol, Pyrazinoquinoxaline, Amino dithioacetals, Applications.

## Introduction

Pyrimidines are chief aromatic N-heterocycles of both chemical and mechanistic interest found in nature. Eloquently, the chemistry of pyrimidines has been investigated for decades together and several reviews have appeared [1]. Pyrimidine and their derivatives have a long and notable history and occupy a central position in the medicinal world. The important pyrimidine compounds have diverse applications like bactericidal,[2] fungicidal,[3] analgesic,[4] anti-inflammatory, [5] antitumor agents, [6] antioxidant, [7] and anti-HIV, [8]. They are also used as a calcium channel blocker. Pyrimidines occur in some pesticides and plant growth regulators. The pyrimidine derivatives are of significant importance due to their structural diversity and a wide range of applications. The presence of various substituents on the heterocyclic core allows to efficiently vary their biological activity [9-11].

The pyrimidine fragments are of unexpected interest for medicines as they covalently bind to amino acid residues of proteins, thereby allowing their usage for covalent inhibition of various proteins. The cyano pyrimidine-based compounds are efficient inhibitors of cysteine protease [12,13]. Recent work on pyrimidine compounds has inspired the researchers due to their potential activity against SARS-CoV-2 corona virus, which is responsible for the COVID-19 pandemic [14]. It is critical to highlight, that molnupiravir, which is one of the exhaustively activated agents to treat COVID-19, also contains a pyrimidine ring 15-18]. This ring is responsible for tautomeric transformations in molnupiravir, which is one of the important factors for determining its antiviral properties [19].

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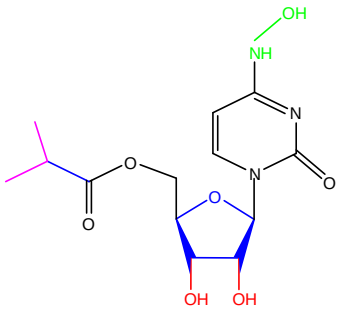
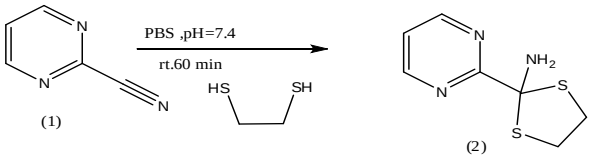



**Figure 1:** Molnupiravir an oral antiviral drug for the treatment of COVID-19

*N*-heteroacenes are distinguished π-conjugated scaffolds for both *n*- and *p*-type organic semiconductors [20-23]. A wide range of electronic and liquid-crystalline properties of several electron-accepting 1,4-dihydropyrazinoquinoxalinediones along with different synthetic transformations have been reported. The incorporation of strong hydrogen-bonding interactions has expedited the formation of a highly ordered liquid-crystalline phase within these systems,[24]. In this article authors have suggested/proposed mechanism for a range of pyrimidine and pyrazino quinoxaline derivatives. Although the compounds are known but the developed mechanisms have not been reported or discussed earlier as revealed by the exhaustive literature survey. Apart from this, an extensive variety of emerging applications of pyrimidine derivatives and allied nitrogen heterocycles have also been outlined in this article.

## Discussion

The structural diversity and biological importance of nitrogen heterocycles have made them attractive synthetic targets over many years and are found in various natural products. Pyrimidine pharmacophore is an important and integral part of DNA and RNA and plays an essential role in several biological processes. Pyrimidines occupy an outstanding position in organic and medicinal chemistry for their high biological activity. The pyrimidine core is a structural constituent of critically important drugs like Fluorouracil, Etravirine, Risperidone, Iclaprim, Avanafil, and Rosuvastatin [25]. Nitrile derivatives of pyrimidines are promising reagents for bioconjugation due to their high electrophilicity and selectivity for reaction with thiols. The reaction of heteroaryl nitriles with bis-thiols has been explored to generate stable amino dithioacetals (ADTA, s), which could facilitate new bioconjugation protocols. In an interesting reaction, 2-cyano pyrimidine **1** has been used as a model electron deficient nitrile substrate which when allowed to interact with 1,2-ethane dithol under aqueous buffered conditions (pH 7.4), rapidly afforded the desired product ADTA **2** in excellent yields.




**Scheme 1.** Synthesis of compound (2)

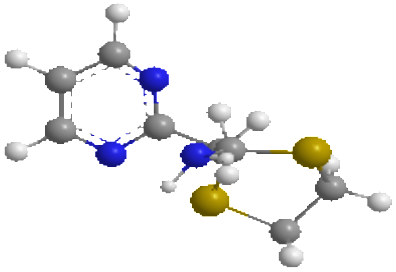
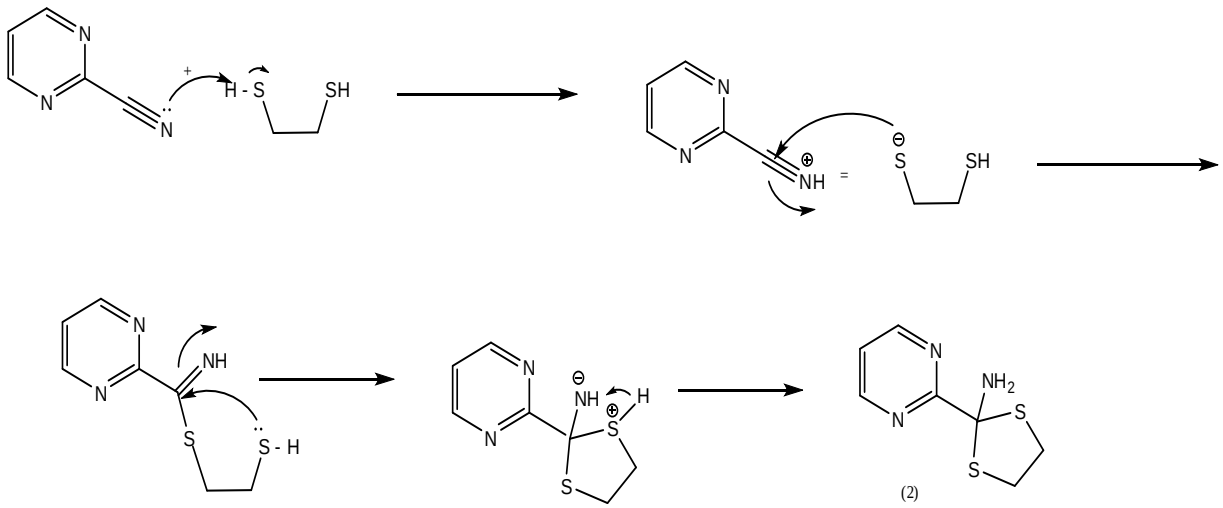


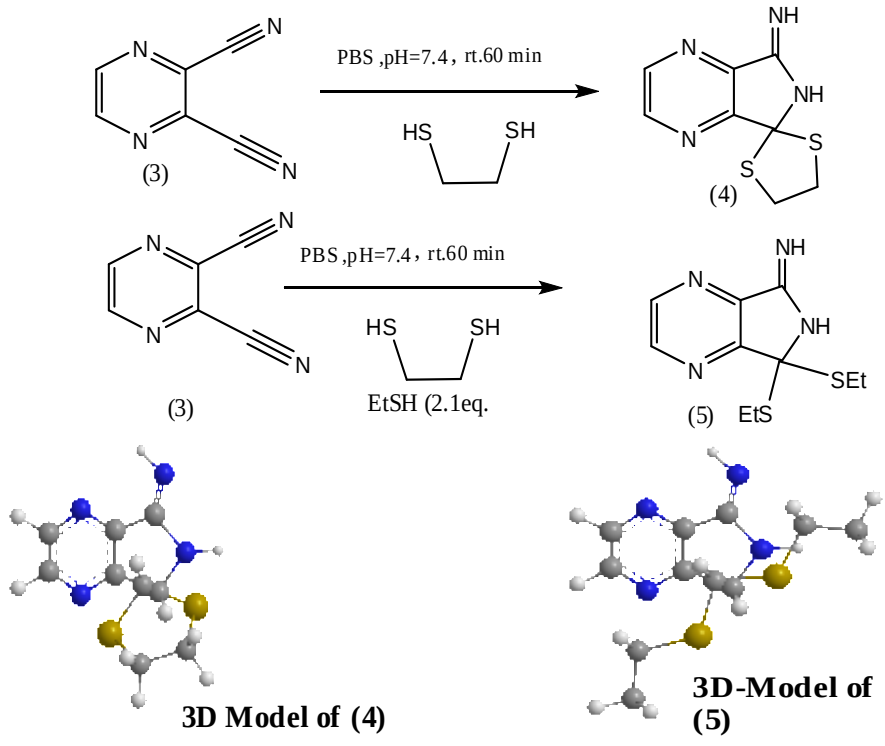
**Figure 2.** 3D Model of (2)

As revealed by literature survey the mechanism of this reaction is not known, therefore a plausible mechanism has been proposed for the formation of **2** as below (Scheme 2).



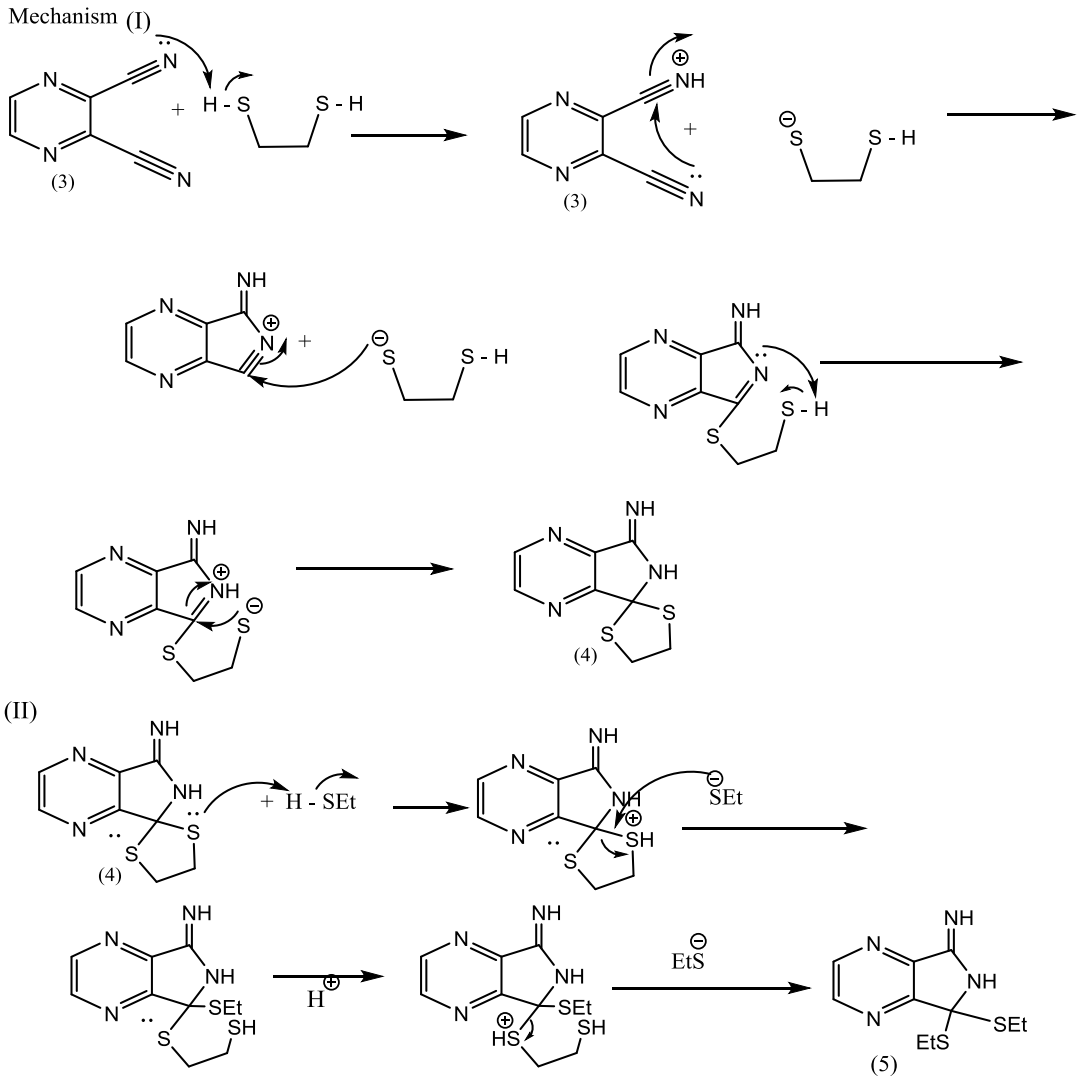

**Scheme 2.** Mechanism developed for the formation of amino dithioacetal **(2)**

In a cascade reaction observed with pyrazine bis-nitrile, ADTA amine gets trapped by the second nitrile to form cyclic dithio products **4** and **5 (Scheme 3).**




**Scheme 3.** Synthesis of compounds **4** and **5**

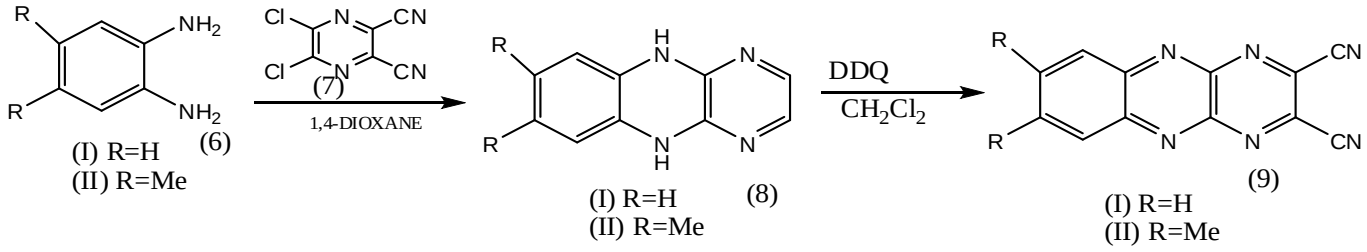
Mechanism developed for the formation of **4** and **5** can be justified as below (Scheme 4).




**Scheme 4.** Mechanism proposed for the formation of (4) and (5)

Pyrazine bis-nitrile **3** has been identified as a convenient substrate as the second nitrile easily facilitates an intramolecular cyclization. This unique reaction of pyrazine **3** with a bis- or monothiol afforded ADTAs **4** and **5** in very high yields.

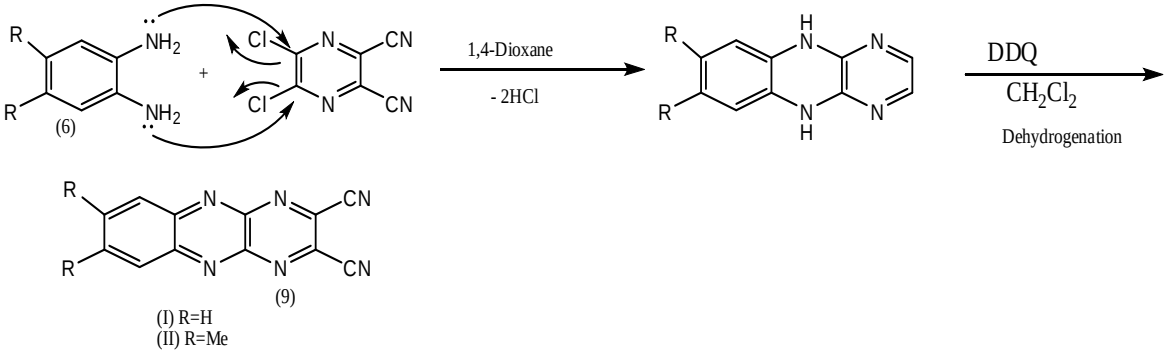
Pyrazinoquinoxaline is another important member of class of nitrogen heterocycles. A wide range of dicyanopyrazinoquinoxalines (DCPQs) **9-12** have been synthesised when o-phenylene diamine **6** and allied compounds were interacted with pyrazine derivatives (Scheme 5).



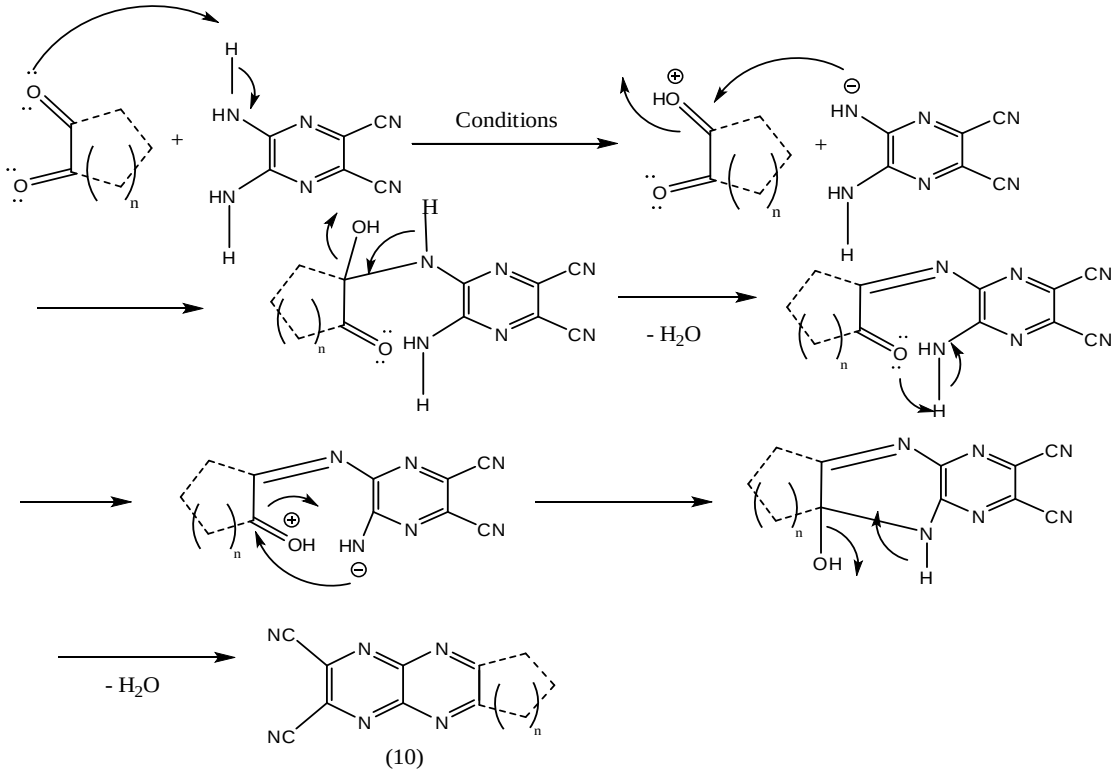

**Scheme 5.** Synthesis of compounds **9**-12

Comprehensive literature survey revealed that the mechanism of formation for the compounds **9-12** is not known, therefore, the plausible mechanism suggested for these compounds can be rationalised as below (Scheme 6).

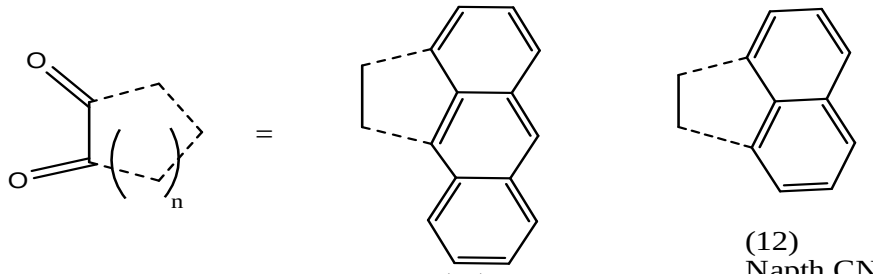
I.



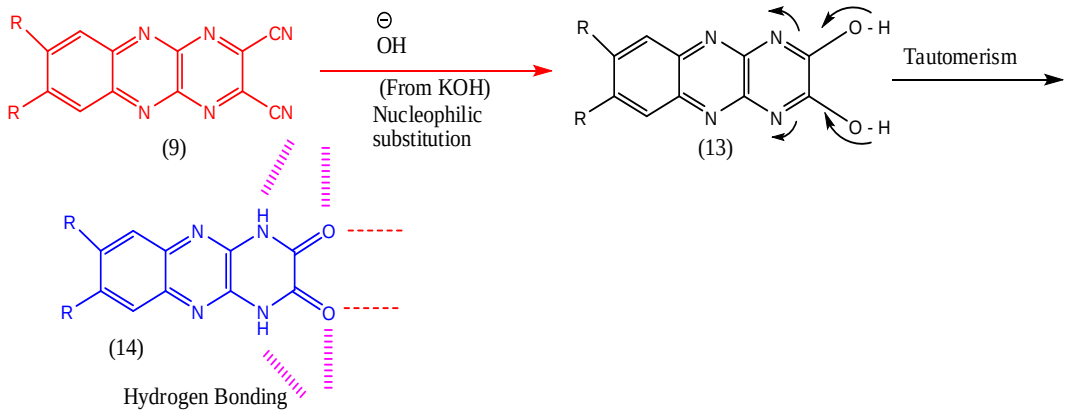

II-




**Scheme 6.** Mechanism suggested for the compounds **9-10**

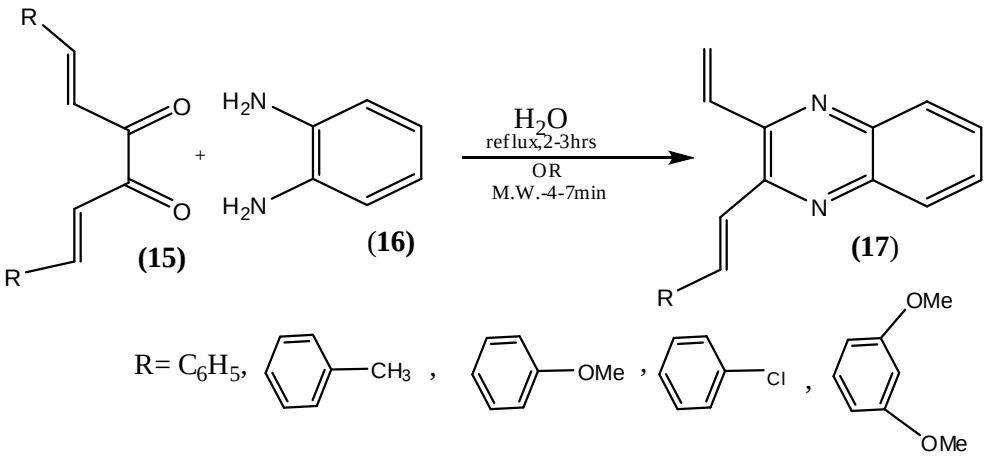


Hydrogen bonding as a directional noncovalent interaction can influence the structural, electronic and optoelectronic properties of bulk materials, [26,27]. This type of interaction plays a vital role in molecular ordering in solid-state organic semiconductors, thereby governing the charge transport pathways and carrier mobilities of both electrons and holes [28-30]. The electronic characteristics and liquid-crystalline properties of 1,4-dihydropyrazinoquinoxalinediones have been reported. The incorporation of strong hydrogen-bonding interactions facilitate the formation of a highly ordered liquid-crystalline phase within this system-(Scheme 7)



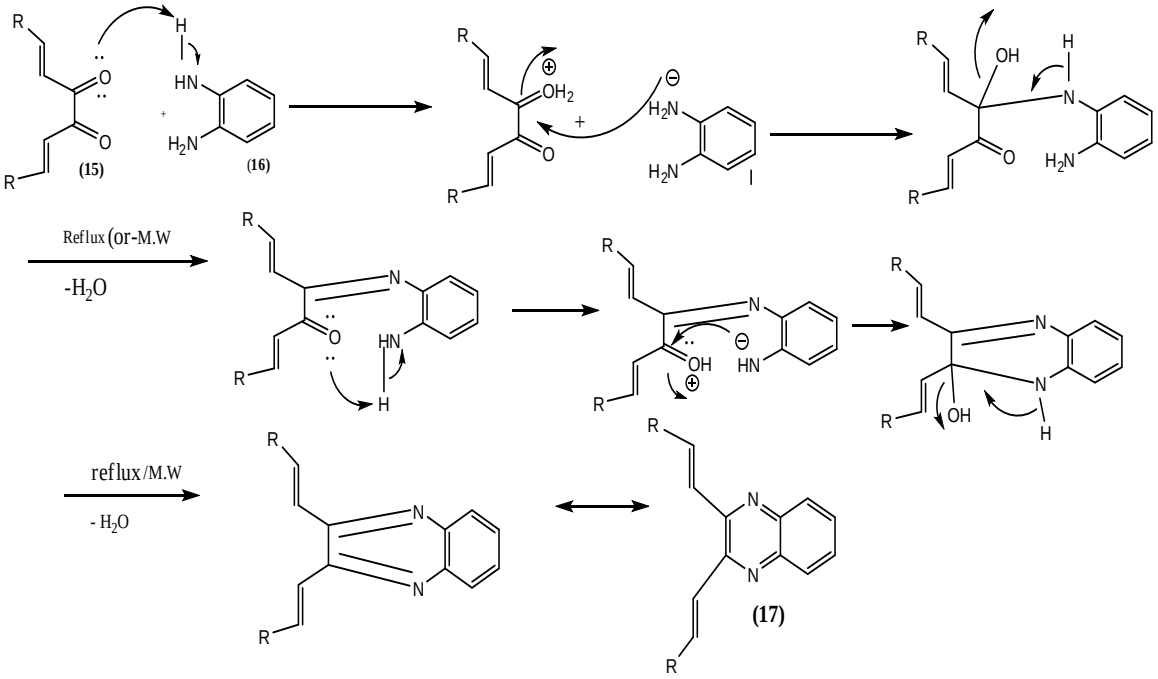

**Scheme 7:** Transformation of DCPQ,s to H-bonding capable DPQD derivatives

In an interesting reaction, a simple and convenient method for the synthesis of quinoxaline derivatives **17** has been developed from cinnamils **15** in water under reflux/microwave irradiation conditions. (Scheme 7).



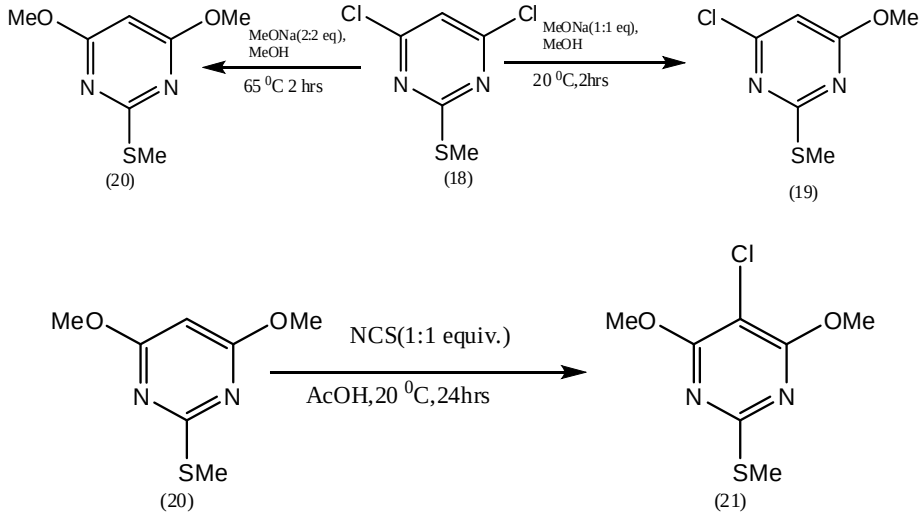

**Scheme 7.-** Synthesis of quinoxaline derivatives **17**

Probable mechanism developed for the formation of quinoxaline derivatives **17** is analogous to that proposed for the formation of compound **10** and can be discussed as below (Scheme 8).



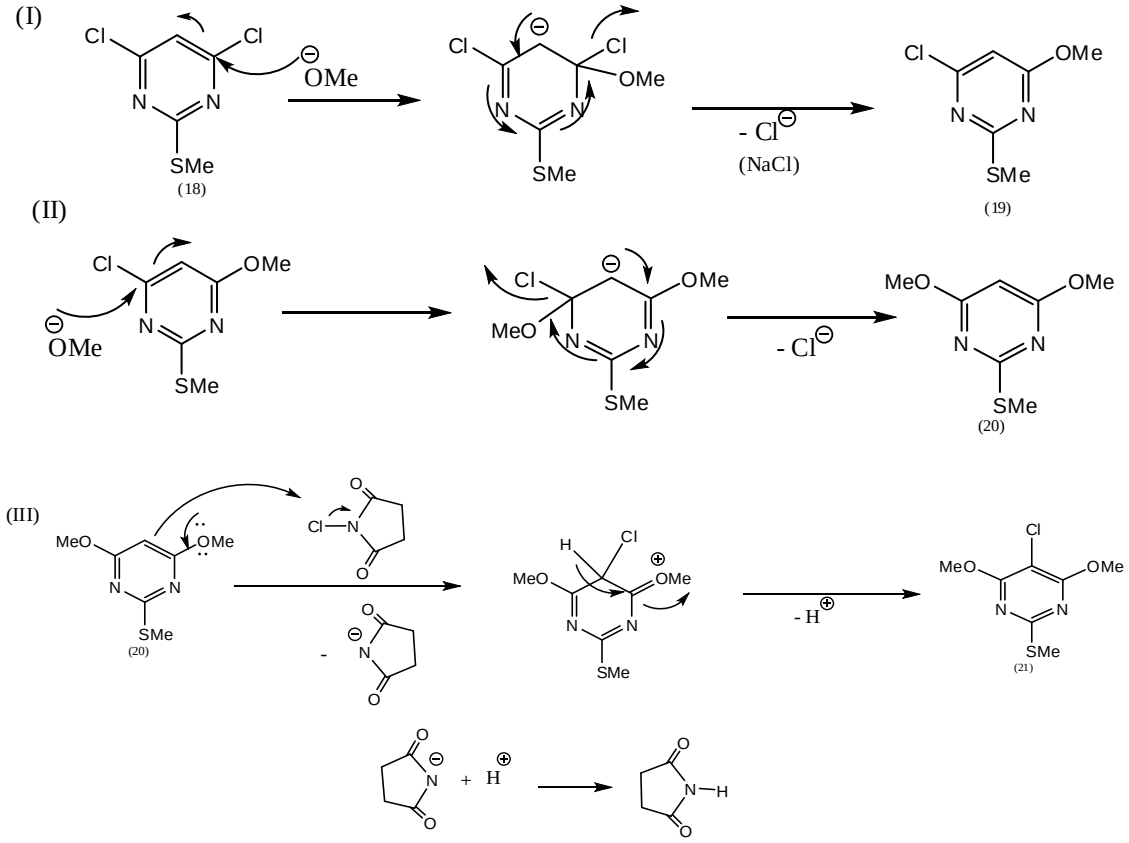

**Scheme 8.** Mechanism developed for the formation of quinoxaline derivatives 17

In a similar reaction 4,6-Dichloro-2-(methylthio) pyrimidine **18** has been converted to 4-chloro-6-methoxy-2-(methylthio) pyrimidine **19** and 4,6-dimethoxy-2 (methylthio)pyrimidine **20**. However, chlorination of the latter with N-chlorosuccinimide (NCS) affords 5-chloro-4,6-dimethoxy-2-(methylthio) pyrimidine **21** in good yield [31,32] (Scheme 9).




**Scheme 9.** Conversion of 4,6-Dichloro-2-(methylthio) pyrimidine **(18)** to its derivatives **(19), (20)** & **(21)**

Literature survey discloses that the mechanism for these compounds is not known; therefore, the most possible mechanism proposed for these compounds is depicted below (Scheme 10).



**Scheme 10.** Mechanism proposed for the formation of compounds **(19),(20)& (21)**

## Emerging Applications of Pyrimidine and Pyrazinoquin-oxaline derivatives

Pyrimidines, a broad class of nitrogen heterocycles, have received considerable attention due to their wide range of biological activities such as anti-inflammatory, anti-cancer, anti-allergic, analgesic etc. Alzheimer's disease is a major public health issue and will apparently be the most important disease in developed/developing countries. A series of *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines and their pyrido and pyrazino analogues have been tested and found potent against the disease. 1,2,3-triazole–pyrimidine–urea derivatives have been synthesized and evaluated for anticancer activity. Epilepsy is the third most devastating neurological disorder affecting millions people globally. A range of new substituted pyrimidine synthesized derivatives have appeared for their anticonvulsant potential. 5-alkoxytetrazolo [1,5-*c*] thieno [2,3-*e*] pyrimidine derivatives also proved for their anticonvulsant activity. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the major causes for chronic liver diseases in humans. A new class of pyrimidine nucleosides possessing a 40-carboxymethyl and 40-carboxamide functional group have been reported for their anti-HCV activity. Inflammation is a characteristic of many diseases and may sometimes lead to various diseases like arthritis, atherosclerosis, diabetes and even cancer [33].A large number of pyrimidine derivatives synthesised by Suzuki cross coupling, acid amination, and reduction are found to be potent antiinflammatory agents. 4-aminoquinoline pyrimidines reported are characterized and evaluated for their anti- malarial potential and found active. Prevalence of fungal and bacterial infections has increased dramatically. The universal use of antifungal and antibacterial drugs and their resistance against respective infections has led to serious health issues. A library of 4-(4-(arylamino)-6-(piperidin-1-yl)-1,3,5-triazine-2-ylamino)-*N*-(pyrimidin-2-yl) benzene sulphonamide analogs have been synthesised and evaluated them for their *in vitro* antimicrobial activity. A sizable number of these synthesized compounds exhibit significant antimicrobial activity on several strains of microbes.

Pyrazinoquinoxaline is an important member of class of nitrogen heterocycles and finds a range of applications in different fields. Its derivatives exhibit affirm biological activities, including antimicrobial, anticancer, and antiviral properties.Pyrazinoquinoxaline's conjugated system find applications in materials science and

dye chemistry. The versatility of pyrazinoquinoxaline contributes to its role in the design of advanced materials for electronic and optoelectronic applications. The quinoxaline derivatives show excellent photo physical properties and stable fluorescence. These derivatives can conveniently be transformed to novel products and find applications in the fields of medicinal chemistry, molecular recognition, organic light emitting devices, optoelectronic devices and *n*-type semi-conducting conjugated polymers. Strong hydrogen bonding interactions effectively modulate energy levels of semiconducting materials, affecting the band gap and charge injection/extraction processes. The incorporation of strong hydrogen-bonding interactions in 1,4 dihydropyrazinoquinoxalinediones facilitates the formation of a highly ordered liquid-crystalline phase within these systems.

## Conclusion

In conclusion, we have developed / suggested a range of mechanisms, which were not known or proposed earlier, for a series of pyrimidine derived amino dithioacetals (ADTAs) and allied dicyanopyrazinoquinoxalines (DCPQ,s) . Besides, an extensive range of emerging applications for these nitrogen heterocycles have also been debated in this article.

## Conflict of interest

Authors declare no conflict of interest.

## Data availability statement

No data sharing is applicable to this manuscript as it is purely a mechanism-based article.

## Acknowledgement

I am highly thankful to University of Kashmir for providing the necessary literature enabling me to compose this new manuscript. I acknowledge to Prof.K.Z.Khan Department of Chemistry University of Kashmir for his valuable and fruitful discussions. I also express my sincere thanks to my colleagues and fellow researchers for their encouragement.

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