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The role of pyrimidines and its derivatives in heterocyclic chemistry

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ABSTRACT

Pyrimidines and their fused derivatives form the heterocyclic core of nucleic acid bases. These ring systems are incorporated into drugs used for AIDS, cancer and anti-viral treatment. The discovery of the anti-HIV activity in AZT containing the pyrimidine nucleus has stimulated a renewed interest in these molecules and has prompted us to focus research on the synthesis and study of biological properties of newer series of pyrimidine derivatives. Several reports have appeared in the literature on the biological activities of carbazole, azacarbazole and quinoline derivatives in the search of newer physiologically active materials from these classes of compounds. Pyrimidine and their myriad derivatives have continued to capture the attention of chemists since their presence in the biologically active materials have been known to produce additive effect on the bio-efficacy of the molecules.

Keywords: AZT, Heterocyclic core, Anti-viral treatment.

1. INTRODUCTION

1.1. Importance of pyrimidine

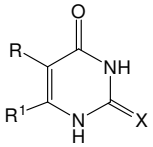
Though hydroxy, mercapto, amino, methyl pyrimidines are relatively less studied heterocyclic systems, but these are of interest in the context of drug development. Pyrimidines bearing these substituents are important as significant number of compounds of this class have been used in synthetic, analytical and medicinal chemistry.

1.2. Biological aspects

Pyrimidines do not exist in nature but their different derivatives, are found to occur in nature as a part of more complex systems and are widely distributed. They have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. They form an integral part of the genetic material Viz. DNA and RNA [1]. Besides, their biological significance, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications like anticancer [2], antibacterial [3], antiprotozoal [4], antimicrobial, antinsecticidal [5], antiviral, antihypertensive [6], antihistaminic [7], anti-inflammatory, analgesic, CNS, active to metabolic, adjuvant [8].

1.3. Antineoplastics and anticancer agents

There are a large number of pyrimidine-based antimetabolites. They are usually structurally related to the endogenous substrates, that they antagonize. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. One of the early metabolites prepared was 5-fluorouracil (5-FU, 1.01a), a pyrimidine derivative. 5-Thiouracil 4.001b also exhibits some useful antineoplastic activities [9,10] (Fig.1).



1.01

Figure – 1: Structure of 5-fluorouracil (1.01a, X=O, R=F.R[1]=H; 1.01b, X=O, R=SH.R[1]=H)

The antineoplastic compounds [11] possessing the guanidine nucleus 1.02 like azathiopurine [12] 1.03, mercaptopurine [13] 1.04, thioguanine [14] 1.05 tegafur [15] 1.06, etc. (Fig.2) were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs prevent the utilization of normal cellular metabolites.

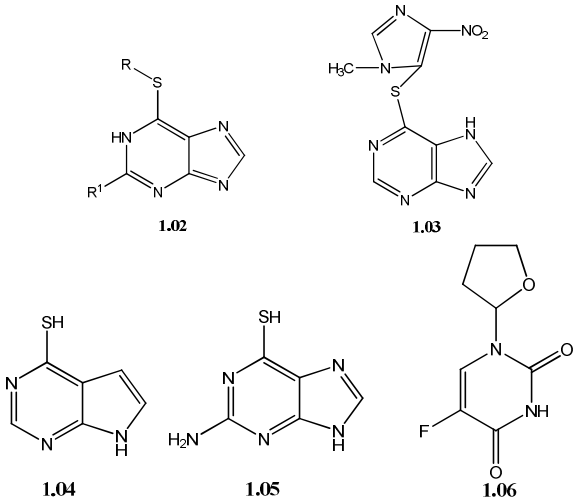


Figure – 2: Structures of antineoplastic compounds possessing the guanidine nucleus.

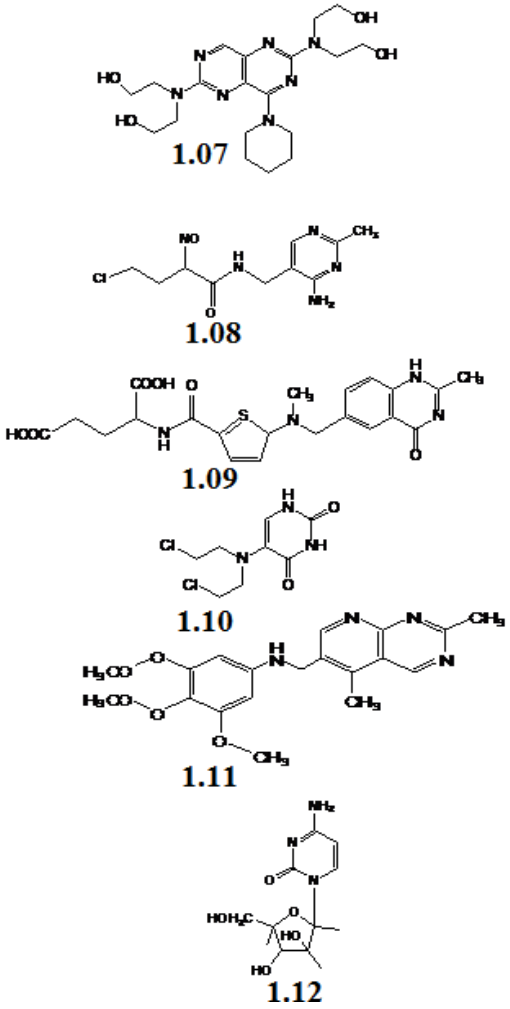


Figure – 3: Structures of antineoplastic compounds possessing the guanidine nucleus.

Many more have been included in recent times, like mopidamol [16] 1.07, nimustine [17] 1.08, reltitrexed [18] 1.09, uramustine [19] 1.10 and trimetrixater [20] 1.11 (Fig.3).

1-β-D-Arabinosylcytosine [21] (Ara-C, 1.12) is also an example of a pyrimidine antimetabolite in which the sugar is arabinose having a beta configuration. It is mainly used as anticancer agents and also exhibits significant therapeutic effects in patients with herpus virus infections and herpus encephalitics. Gemcitabine 1.13, a pyrimidine antimetabolite (Fig.4), shows excellent antitumour activity against murine solid tumours [22].

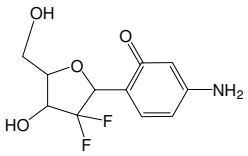
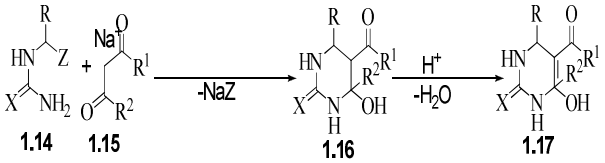


Figure – 4: Structure of 1-β-D-Arabinosylcytosine

1.4. Synthetic aspects

Functionalized heterocycles are interesting scaffolds for the preparation of diversely oriented compound libraries for medicinal and pharmaceutical applications [23-26]. The biological significance of the pyrimidine has led us to synthesise substituted pyrimidine derivatives.Several synthetic strategies have been developed in the literature for the preparation of different analogues of pyrimidine, of which a few examples are given below.

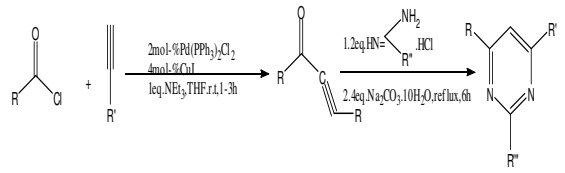
Biginelli compounds [27,28] can be easily prepared by reaction of α-azido or α-tosyl substituted thioureas and ureas 1.14 with sodium enolates of β-oxoesters or 1,3-dicarbonyl compounds 1.15 followed by acid-catalyzed dehydration of the obtained 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones 1.17 [scheme - 1]. Both the stages of the synthesis proceed under mild conditions and usually in high yields. This method is very flexible and gives possibility to prepare a large number of 1, 2, 3, 4-tetrahydropyrimidine-2-thiones/ones bearing various substituents in pyrimidine ring.



Scheme – 1: Preparation of Biginelli compounds

The coupling of acid chlorides 1.18 with terminal alkynes 1.19 using one equivalent of

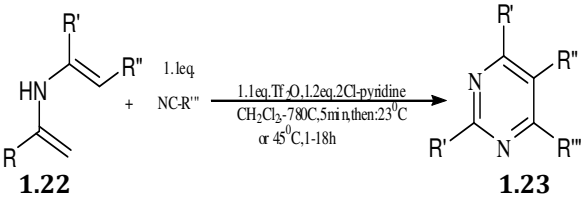
triethylamine under sonogashira conditions followed by subsequent addition of amines or amidinium salts to the intermediate alkynones 1.20 allows a straightforward access to enaminones and pyrimidines 1.21 under mild conditions and in excellent yields [29] [scheme - 2].



1.18 1.19 1.20 1.21

Scheme - 2: Preaparation of enaminones and pyrimidines

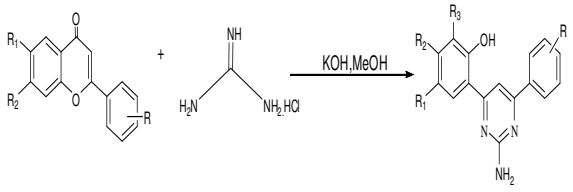
A single-step conversion of various *N*-vinyl and *N*-aryl amides 1.22 to the corresponding pyrimidine 1.23 and quinazoline derivatives involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerization [30] [scheme - 3].



1.22 1.23

Scheme – 3: A single-step conversion of various *N*-vinyl and *N*-aryl amides to the corresponding pyrimidine and quinazoline derivatives.

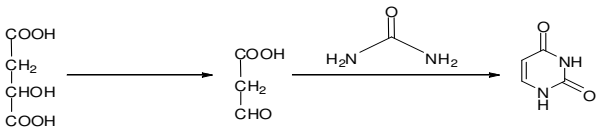
1.24 on condensation with guanidine hydrochloride 1.25 in presence of potassium hydroxide in methanol yield 2-amino pyrimidine 1.26 derivatives [31] [scheme - 4].



1.24 1.25 1.26

Scheme – 4: Preparation of 2-amino pyrimidine 1.26 derivatives

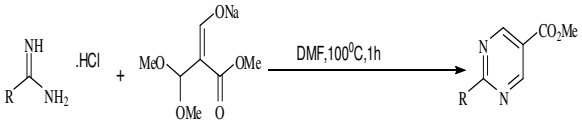
Thymine, uracil and their derivatives are best prepared by the utilization of β–aldehyde and β–ketoesters. The reaction of ethyl formyl acetate 1.28 with urea gets little success but formic acid is generated during the course of the reaction by the oxidative decarboxylation of malic acid, this in turn reacts with urea. By this way, a moderate yield [32] of uracil 1.29 may be obtained [scheme - 5]. Thymine has also been synthesized by a similar route [33].



1.27 1.28 1.29

Scheme – 5: Preparation of uracil

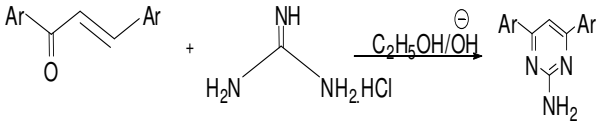
A method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters 1.32 is described. The sodium salt of 3, 3-dimethoxy-2-methoxycarbonylpropen-1-ol 1.31 has been found to react with a variety of amidinium salts 1.30 to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters [34] 1.32 [scheme - 6].



1.30 1.31 1.32

Scheme – 6: Preparation of 2-substituted pyrimidine-5-carboxylic esters.

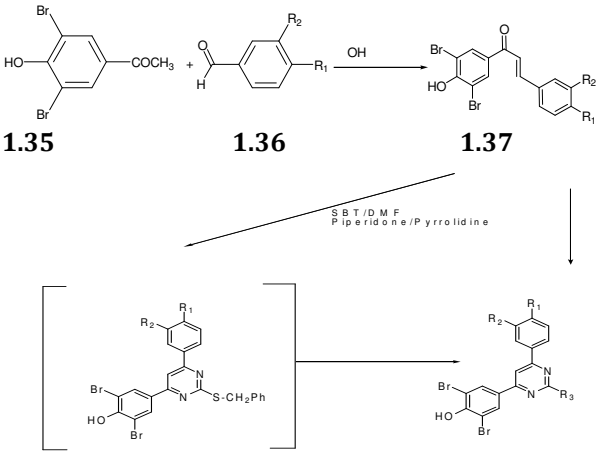
2-Amino-4(4'-anisyl)-6-(3, 4, 5-trimethoxy phenyl) pyrimidine 1.34 can be obtained by the condensation of chalcone 1.33 and guanidine hydrochloride 1.25 in the presence of sodium hydroxide in ethanol [35] [scheme - 7].



1.33 1.25 1.34

Scheme – 7: preparation of 2-Amino-4(4'-anisyl)-6-(3, 4, 5-trimethoxy phenyl) pyrimidine.

3,5-Dibromo-4-hydroxy substituted chalcones 1.37 react with SBT in presence of piperidine/pyrrolidine in DMF to give pyrimidines 1.39 [scheme - 8].

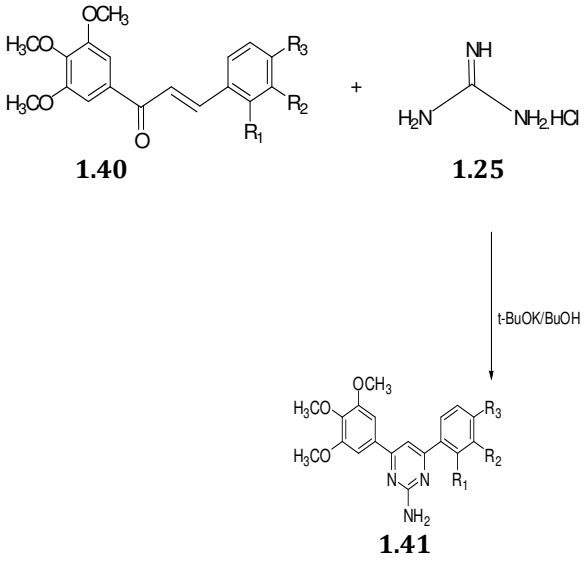


1.35 1.36 1.37

1.38 1.39

Scheme – 8: Preparation of pyrimidines.

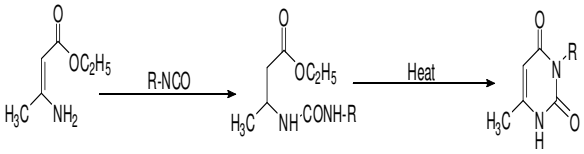
The reaction of chalcones 1.40 with guanidine hydrochloride 1.25 in the presence of potassium tertiary butoxide gives the corresponding pyrimidine derivatives [36] 1.41 [scheme - 9].



1.40 **1.25** **1.41**

Scheme – 9: Preparation of pyrimidine derivatives.

R. Behrend et. Al [37] reported the synthesis of pyrimidine derivatives by condensation of β–cyano or β–acetyl enamine (N-C-C-C fragment which is readily available by direct amination of ethoxymethylene malonic ester derivatives) 1.42 with suitable C-N containing fragments (like β–aminocrotonate) that have been found to undergo extremely facile reaction with phenylisocyanate or methylisocyanate to form intermediate ureido derivatives 1.43, which undergo cyclization on treatment with base to give 1.44 [scheme - 10].

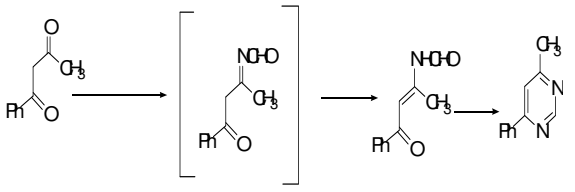


1.42 **1.43** **1.44**

Scheme – 10: Preparation of pyrimidine derivatives by condensation.

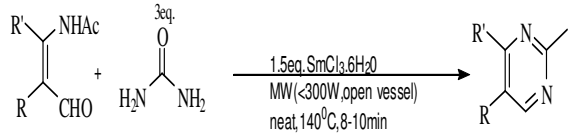
A methylene group activated by a phenyl substitution as simple ketones 1.45 or nitriles are not active enough to initiate the reaction. Such a reaction is carried by reacting β-diketones 1.45 with excess of formamide. The reaction proceeds by the formation of an insoluble β–acylenamidine 1.46 [scheme - 11].

A novel and efficient synthesis of pyrimidine 1.051 from β-formyl enamide 1.049 involves samarium chloride catalysed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation [38] [scheme - 12].



1.45 **1.46** **1.47** **1.48**

Scheme – 11: Preparation of β–acylenamidine.



1.49 **1.50** **1.51**

Scheme – 12: Preparation of pyrimidine.

2. CONCLUSION

In this short review we prepared the different types of derivatives through many types of reactions. And these derivatives are useful in many activities like anti-microbial, anti-fungal and analgesic etc.

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