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SYNTHETIC APPROCHES FOR BIOLOGICALLY ACTIVE PYRIMIDINE - HYDRAZONES

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ABSTRACT

Nowadays, Heterocyclic compounds are proving successful compounds in the field of medicinal chemistry to synthesize various therapeutic compounds. There are enormous biological products developing and present having lots of and different types of pharmacological compounds like anticonvulsants, antimicrobials etc. This study is showing the facts about the synthesis of a heterocyclic compound or combination of such compounds exhibiting pharmacological properties by pyrimidine hydrazones. As we know that pyrimidine nucleus itself having efficiency and potency to exert pharmacological response as it is necessary and important to produce more and more of its variety. Pyrimidines are 6-membered heterocyclic ring compounds composed of nitrogen and carbon. They are present throughout nature in various forms and are the building blocks of numerous natural compounds from antibiotics to vitamins and lipopolysaccharides.

Keywords: Pyrimidine synthesis, Hydrazones synthesis, Chemistry of pyrimidine hydrazones etc.

INTRODUCTION

Medicinal chemistry is the branch of science that deals with the use of techniques and theories of chemistry, molecular chemistry, physics, biology, genetics, information technology and various other fields to discover and synthesize drugs for use in mankind or animals, which exhibiting pharmacological responses [1]. Medicinal chemistry in its most commonly focusing on organic molecules surrounding synthetic organic chemistry and aspects of natural products & computational chemistry together with aim to discover and develop novel and diverse therapeutic agents, which have positive and desired pharmacological effect. In addition to this it involves various chemical aspects of identification, study of physicochemical properties, and thorough synthetic alteration of new chemical entities to make them suitable for therapeutic use. The process is also called bioisosterism which includes synthetic and computational aspects of the study of existing molecule in development in relation to their bioactivities i.e., understanding their structure-activity relationships (SAR) [2].

Objectives

This study is showing the facts about the synthesis of a heterocyclic compound or combination of such compounds exhibiting pharmacological properties by pyrimidine hydrazones. As we know that pyrimidine nucleus itself having efficiency and potency to exert pharmacological response as it is necessary and important to produce more and more of its variety.

Introduction of drug discovery

Drug discovery is the research to produce novel therapeutic products or to modify already existing one which includes therapeutic correlations between the biological target that a drug modulates and the disease that it attempts to manage .In the most crucial and expensive phase 3 trials, drugs that use a novel mechanism [3].

Pyrimidine

Pyrimidines are 6-membered heterocyclic ring compounds composed of nitrogen and carbon. They exist enormously in various forms and are the building blocks of various natural or synthetic or semi-synthetic compounds from antibiotics to vitamins and liposacharides.

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The most commonly recognized pyrimidines are the bases of RNA and DNA, the most abundant being cytosine, thymine or uracil. The origin of the pyrimidine is since 1884 by a Scientist named Pinner. The structure and chemical or physical properties can be described as following [4].

Chemical Properties of Pyrimidine

A pyrimidine has many properties similar with that of pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. Reduction in resonance stabilization of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions [5].

Types of Pyrimidine

Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives [6].

Reactions of Pyrimidine

Perhalogenated pyrimidine scaffolds. Reactions of 5-chloro-2, 4, 6-trifluoropyrimidine with nitrogen centered nucleophiles.[7] Highly functionalized pyrimidine derivatives are important to the life-science industries and there exists a need for efficient synthetic methodology that allows the synthesis of polysubstituted pyrimidine derivatives that are regioselective in all stages to meet the demands of RAS techniques for applications in parallel synthesis. 5-Chloro-2, 4, 6-trifluoropyrimidine may be used as a scaffold for the synthesis of polyfunctional pyrimidine systems if sequential nucleophilic aromatic substitution processes are regioselective. Pyrimidines are electron-deficient aromatic systems and, when halogenated, become very useful substrates for a variety of nucleophilic aromatic substitution (SNAr) processes & since several chloro pyrimidines are commercially available, there have been many reports of synthetic strategies concerned with creating pyrimidine-based libraries from halogenated core scaffolds. Reactions of amine nucleophiles with 5-chloro-2, 4, 6-trifluoropyrimidine

Pharmaceuticals with pyrimidine sub-units [7]
Hydrazone

It is a class of organic compounds with the structure $R_1R_2C{=}NNH_2$. They are related to ketones and aldehydes by the replacement of the oxygen with the NNH_2 functional group. They are formed usually by the action of hydrazine on ketones or aldehydes. They are well known for their, antioxidant, antimicrobial, antimalarial, antiviral activities, and if they are allowed to fuse with Pyrimidine they produce CNS activity too. Therefore the above data clearly showed that pyrimidine hydrazones are potent biologically active compounds. Therefore a need was felt to synthesize newer pyrimidine hydrazones.

Reactions of Hydrazones

Hydrazones are reactants in hydrazone iodination, the Shapiro reaction and the Bamford-Stevens reaction to vinyl compounds. A hydrazone is an intermediate in the Wolff–Kishner reduction. Another method to synthesis a hydrazone is the Japp–Klingemann reaction (from β-keto-acids or β-keto-esters and aryl diazonium salts). In N, N′-dialkylhydrazones the C=N bond can be hydrolyzed, oxidized and reduced; the NN bond can be reduced to the free amine. The carbon atom if the C=N bond can react with organometallic nucleophiles. The alpha-hydrogen atom is more acidic by 10 orders of magnitude compared to the ketone and therefore more nucleophilic. In asymmetric synthesis SAMP and RAMP are two chiral hydrazines that act as chiral auxiliary with a chiral hydrazone intermediate [8].

Uses

Formation of aromatic hydrazone derivatives is used to measure the concentration of low molecular weight aldehydes & ketones. For e.g., dinitrophenylhydrazine coated onto silica sorbent is the basis of an adsorption cartridge [9].

Base-Mediated Reaction of Hydrazones and Nitroolefins with Reversed Regioselectivity

A regioselective synthesis of tri- or tetra substituted pyrazoles by the reaction of hydrazones with nitroolefins mediated with strong bases such as t-BuOK exhibits a reversed, exclusive 1, 3, 4- Regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields [10].

Pharmaceuticals with Hydrazones sub-units
Formation of Hydrazones or Wolf-Kishner Reduction

The reaction begins with hydrazone formation. Hydrazone formation results from the reaction of the ketone with $_2HN\text{-}NH_2$ (hydrazine). This reaction is like the formation of an oxime with the C=O except that $_2HNNH_2$ is used instead of $_2HN\text{-}OH$ [11].

Literature Review (Synthesis of Pyrimidines) [12]
Hydrazone Synthesis [13,14]

Figure 1. Structure of Pyrimidine

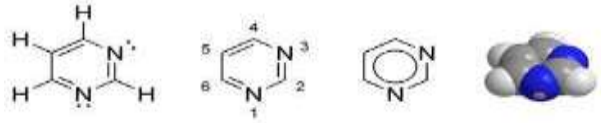


Figure 2. Structure of Pyrimidine [4]

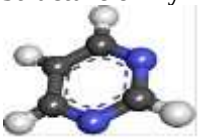


Figure 3. Types of Pyrimidine [6]

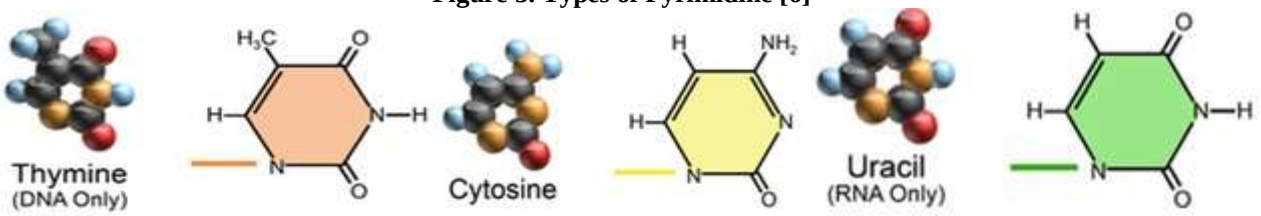


Figure 4. Reactions of Pyrimidine [7]

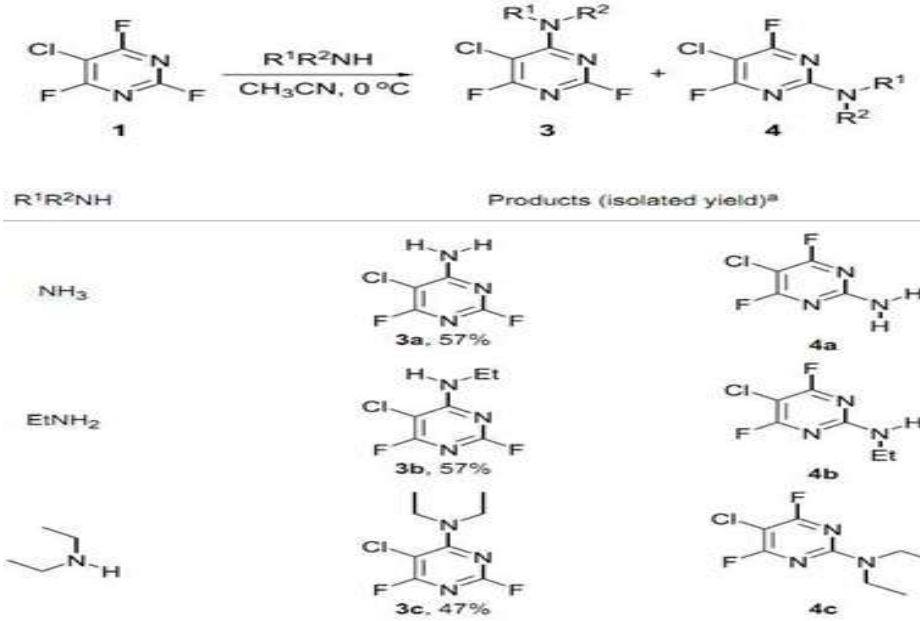


Figure 5. Pharmaceuticals with pyrimidine sub-units [7]

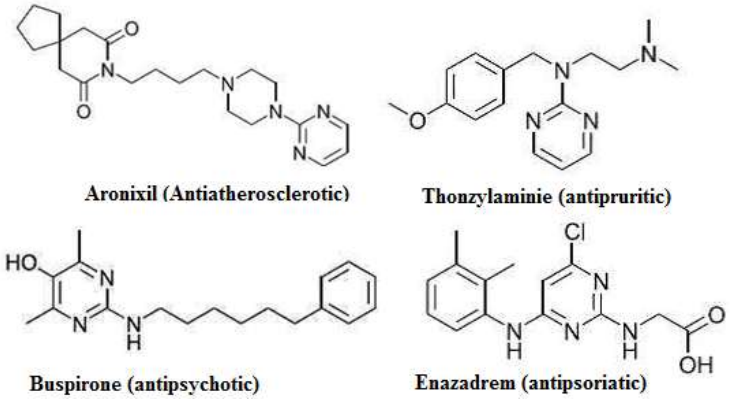


Figure 6. Pharmaceuticals with pyrimidine sub-units [8]

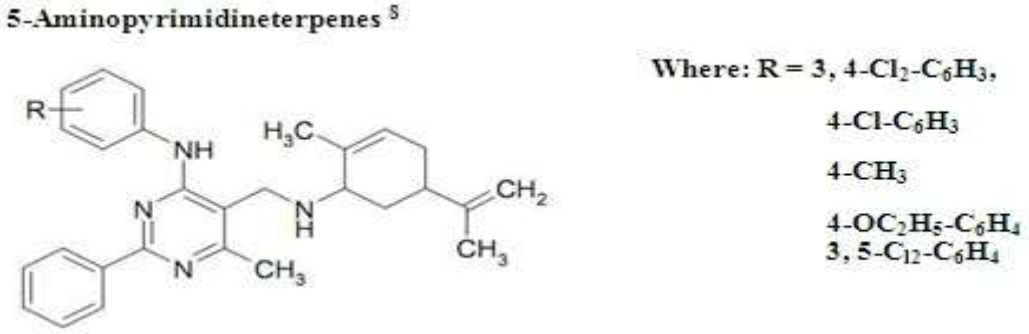


Figure 7. Structure of Hydrazone [9]

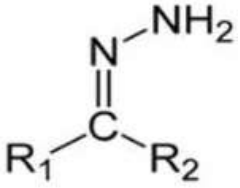


Figure 8. Reactions of Hydrazones

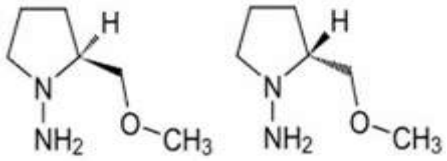
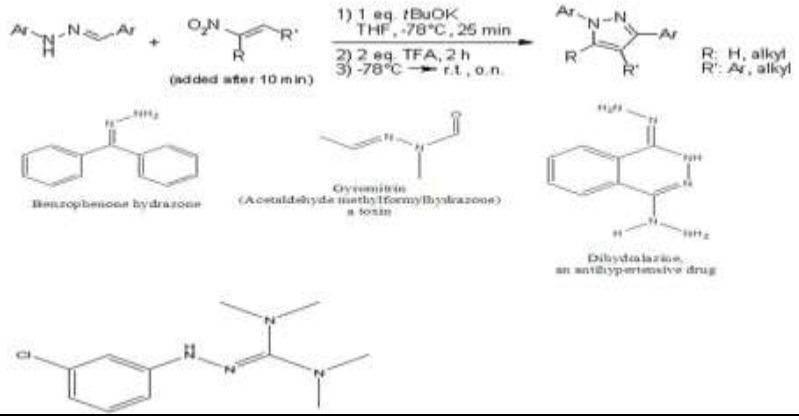
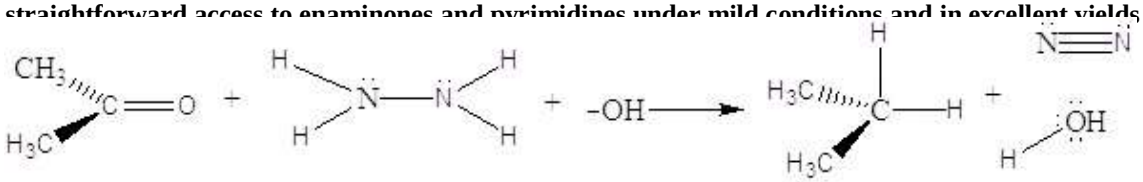


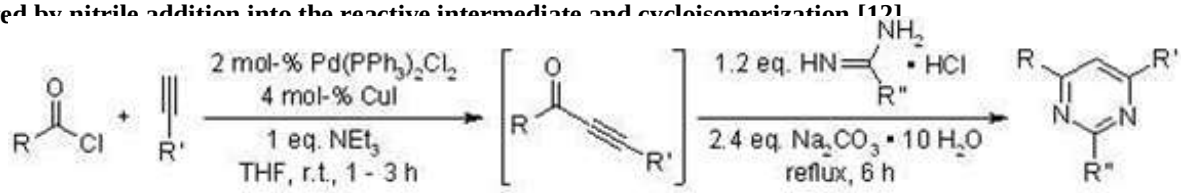
Figure 9. Pharmaceuticals with Hydrazones sub-units [10]



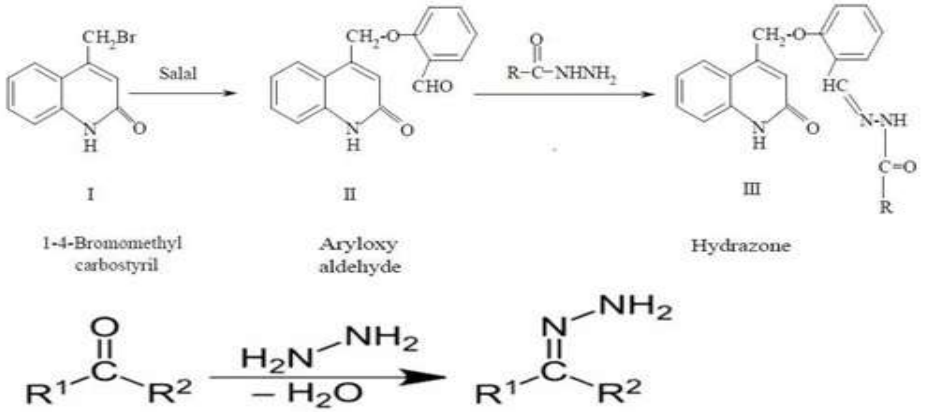
Scheme 1. The coupling of acid chlorides with terminal alkynes using one equivalent of triethylamine under Sonogashira conditions followed by subsequent addition of amines or amidinium salts to the intermediate alkynones allows a straightforward access to enaminones and pyrimidines under mild conditions and in excellent yields [11]



Scheme 2. A single-step conversion of various N-vinyl and N-aryl amides to the corresponding pyrimidine and quinazoline derivatives involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerization [12]



Scheme 3. General Synthesis of Hydrazones [13,14]



CONCLUSION

This study is showing the facts about the synthesis of a heterocyclic compounds have great potency in the field of medicinal chemistry to synthesize various therapeutic compounds with lots of pharmacological activities and to produce. There are different types of pharmacological compounds which are efficienct, potent enought to exert desired pharmacological response. Now it became very important topic of research to prepare various bioisosteres with the pyrmidine hydrazones as basic moiety.

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CONFLICT OF INTEREST: None.

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