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REVIEW ARTICLE

BIOLOGICALLY ACTIVE PYRIMIDINE HYDRAZONES

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ABSTRACT

Pyrimidine constitutes an important class of heterocycles in drug discovery & is very well known for their anticancer, antimicrobial, antioxidant & antiviral activities. **Hydrazones** is a class of organic compounds with the structure $R_1R_2C=NNH_2$. They are formed usually by the action of hydrazine on ketones or aldehydes & have efficient CNS depressant, analgesics activity. In the same context, **Schiff bases** of pyrimidine hydrazones can be prepared by the reaction of "4-(4-Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid hydrazide" with various terpenes such as **citral, camphor, furfuraldehyde & menthone** to make **Schiff bases** individually by refluxing them in the presence of glacial acetic acid (as solvent) for at least 2hrs to yield their respective derivatives.

The present studies revealed that Pyrimidine hydrazone derivatives could be used to synthesize the compounds having potent biological activities such as anticancer, antimicrobial, antioxidant, CNS depressant, analgesic & antiviral activities. All the prepared derivatives were under investigation for their antimicrobial activity and likely to possess the same & desired action.

Keyword: Pyrimidine Hydrazones, Biological active Pyrimidine, Schiff Bases etc.

1. INTRODUCTION

Medicinal chemistry is the branch of science that deals mainly with the synthetic organic chemistry and pharmacology of the drugs with special references to structure including design, modifications and analysis of drugs or chemical synthesis of lead compounds to make them suitable for the mankind or animals with least toxicity and optimum response¹.

Heterocyclic chemistry is a very important branch of organic chemistry and most of the organic synthetic or semi synthetic compounds are heterocyclic in structural properties. Its structure can be described with carbon atoms in ring forming carbocyclic compound².

The most common heteroatoms are Nitrogen, oxygen and sulfur. But heterocyclic rings containing other hetero atoms are having in broad variety. Heterocyclic compounds can be classified as aliphatic and aromatic.

The aliphatic heterocyclics are the cyclic similarities of amines, ethers, thio ethers, amides, etc.

Heterocyclic compounds are having importance in various medicinal formulations and are present in a large variety of drugs, most vitamins, natural products etc. In addition to this biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, anticonvulsant, and insecticidal agents³.

1.1 Pyrimidine

Heterocyclic aromatic organic compound like benzene or pyridine, having two nitrogen atoms at positions 1 and 3 of the six-membered ring; they have isomers in the forms of diazine⁴

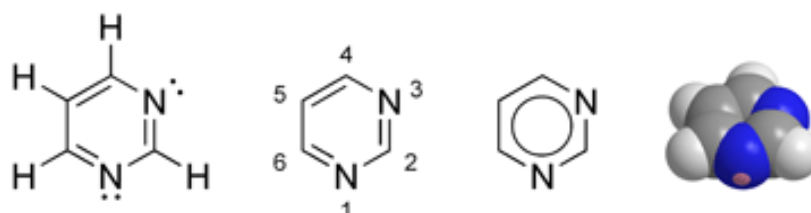


Figure 1

IUPAC Name:

1, 3-Diazine, m-Diazine

Formula:

 $C_4H_4N_2$

Molecular Mass:

80.088 g mol⁻¹

Density:

1.016 g cm⁻³

Solubility:

Alcohol, Water

Melting Point:

20-22 °C

1.2 Types of Pyrimidine

Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives:^[4]

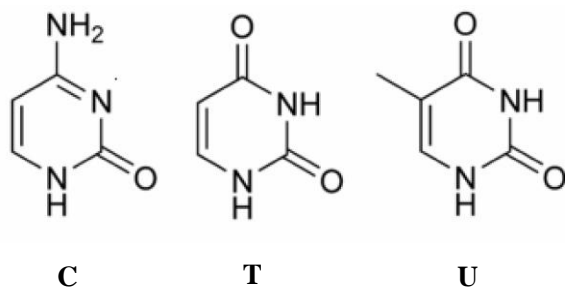
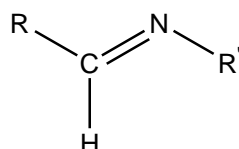


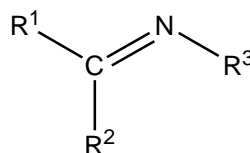
Figure 2

1.3 Hydrazones

An organic compounds having structure of $R_1R_2C=NNH_2$ and are associated to ketones and aldehydes by substitution of the oxygen by means of NNH_2 functional group. They are designed basically by the feat of hydrazine on ketones or aldehydes⁵.



General structure of a Schiff base

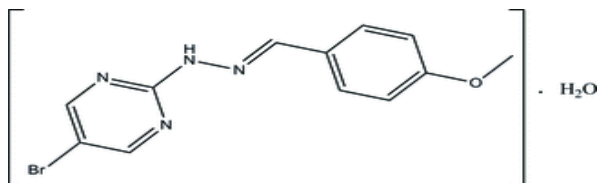


General structure of an azomethine

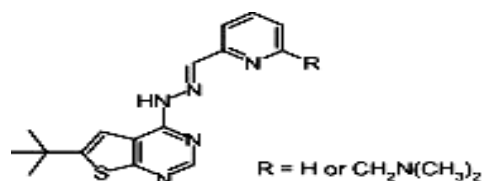
Figure 4

1.5 Some Compounds Having Pyrimidine Hydrazones

a). 4-methoxybenzaldehyde (5-bromopyrimidin-2-yl) hydrazone monohydrate⁷. Pyrimidine and their derivatives possess biological and pharmacological activities such as antibacterial, antimicrobial, anti-inflammatory, analgesic, anticonvulsant and anti-aggressive properties

 $C_{12}H_{11}BrN_4O \cdot H_2O$ 

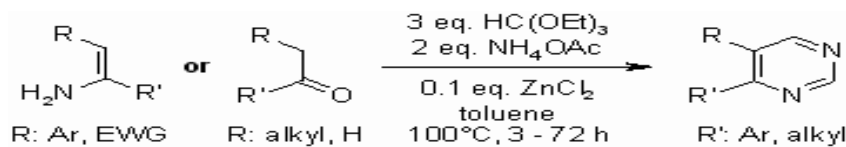
b). Novel thieno [2, 3-d] pyrimidin-4-yl Hydrazone-based Cyclin D1-CDK4 inhibitors⁸



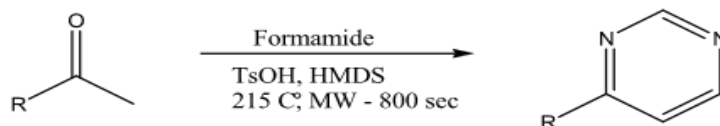
2. CHEMICAL APPROACHES

2.1 Pyrimidine

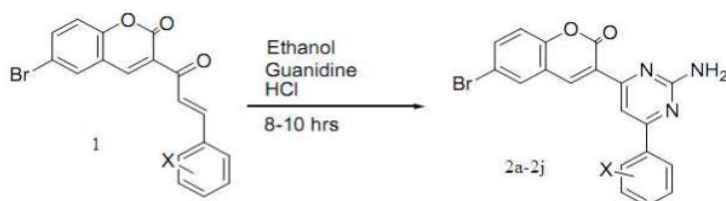
2.1.1 Scheme-1: $ZnCl_2$ -catalyzed three-component coupling reaction allows the synthesis of various 4, 5-disubstituted pyrimidine derivatives in a single step from functionalized enamines, triethylorthoformate, and ammonium acetate. The procedure can be successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines⁹



2.1.3 Scheme-2: Synthesis of pyrimidines from ketones using microwave irradiation¹⁰



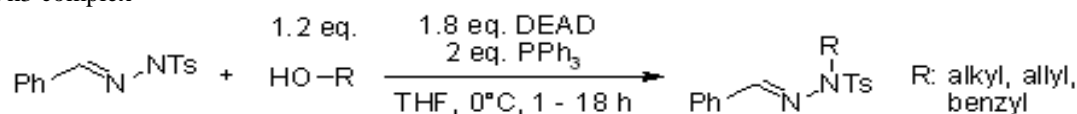
2.1.3 Scheme 3: Synthesis, analgesic and ulcerogenic activity of novel pyrimidine derivative of coumarin moiety: A novel series of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (2a-2j) was synthesized from 3-acetyl-6-bromo-2H-chromen-2-one¹¹



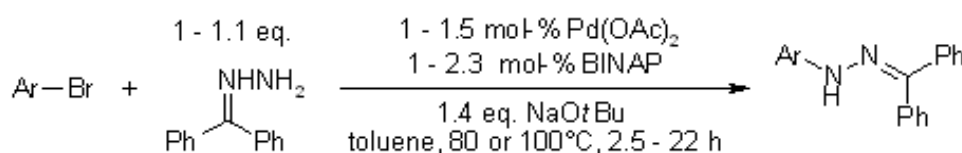
X=2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-OCH₃, 3-OCH₃, 2,4-Dichloro, 2,6-Dichloro

2.2 Hydrazone

2.2.1 Scheme 4: Tosyl- and Boc-hydrazones were found to be effective nucleophiles in the Mitsunobu reaction. Tosyl hydrazones reacted cleanly with primary and secondary alcohols when co-administered to a cooled DBAD/PPh₃ or DEAD/PPh₃ complex¹²



2.2.2 Scheme-5: Central to an alternative source of substrates for Fischer indolizations was a palladium-catalyzed coupling to prepare N-aryl benzophenone hydrazones. Hydrolysis of the hydrazones in the presence of ketones produced enolizable hydrazones that underwent Fischer indolization¹²

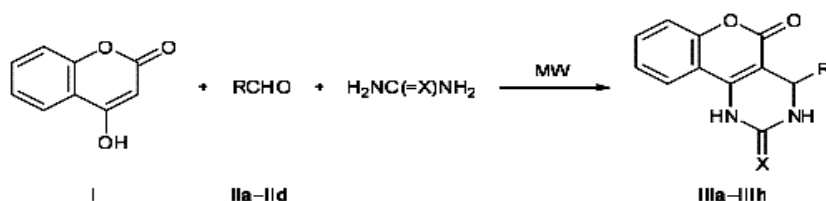


3. BIOLOGICAL ACTIVITY APPROACHES

3.1 Pyrimidine

3.1.1 Biologically Active Pyridopyrimidines:

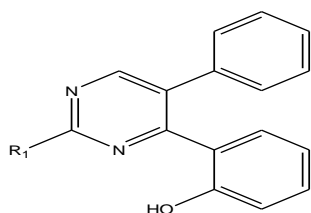
The compounds below have efficient analgesics, CNS depressant activity, and in spite of that it also exhibit antibacterial & antifungal activity¹³



II, R = Ph (a), 1,3-2H-benzodioxol-5-yl (b), 3-indolyl (c), 2-chloroquinolin-3-yl (d); III, R = Ph (a, b), 1,3-2H-benzodioxol-5-yl (c, d), 3-indolyl (e, f), 2-chloroquinolin-3-yl (g, h); X = O (a, c, e, g), S (b, d, f, h).

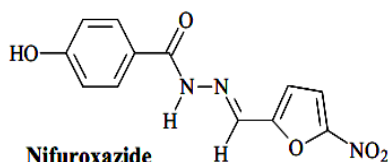
3.1.2 Anti-cancer activity

A series of novel 2, 4, 5-substituted pyrimidine derivatives were synthesized and evaluated for inhibition against the human hepatocellular carcinoma BEL-7402 cancer cell line¹⁴



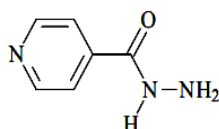
3.2 Hydrazone

There has been considerable interest in the development of novel compounds with anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumor, vasodilator, antiviral & antischistosomiasis activities¹⁵



Nifuroxazide

Antibiotic, Antidiarrheal

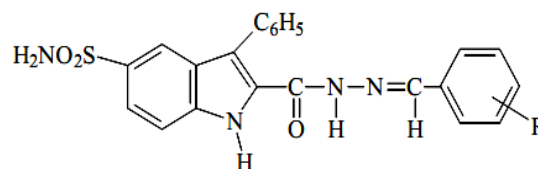


Isoniazid

Anti-tubercular

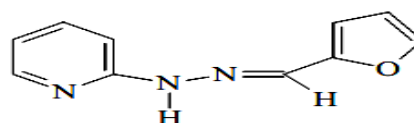
3.2.1 Anti-Depressant Activity

New arylidenehydrazides which were synthesized by reacting 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes, evaluated for their antidepressant activity¹⁵



3.2.2 Analgesic, anti-inflammatory & antiplatelet activity

Derivative 2-(2-formylfuryl) pyridylhydrazone presented a 79 % inhibition of pleurisy at a dose of 80.1 $\mu\text{mol/kg}$. The authors also described the results concerning the mechanism of the action of these series of N-heterocyclic derivatives in platelet aggregation that suggests a Ca^{2+} scavenger mechanism¹⁶



4. CONCLUSION

Pyrimidine constitutes an important heterocyclic class in drug discovery & is very well known for their anticancer, antimicrobial, antioxidant & antiviral activities. **Hydrazones** is a class of organic compounds and have efficient CNS depressant, analgesics activity. In the same context, **Schiff bases** of pyrimidine hydrazones are a potent and efficient biological activities such as anticancer, antimicrobial, antioxidant, CNS depressant, analgesic & antiviral activities. There are various synthetic pathways in which various studies are made also to form a potent and efficient Schiff bases and product of pyrimidine hydrazones.

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