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The Simple and Efficient Method of Synthesis of Amino Pyrimidine and Their Derivatives

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Abstract: In the literature survey others reported a variety of synthesis of Pyrimido pyrimidine and their derivatives that have been potential bioactive molecules. Hence, they have to drag considerable attention in the synthesis of biologically active molecule and advanced organic chemistry. In the group of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological, industrial and pharmacological applications such as anticonvulsant, antihypertensive aactivity, analgesic, anti-depressive, antipyretic, anti-inflammatory, Chemotherapeutic agents, antiviral, anti-HIV, antimicrobial and anti-tumour activities. Therefore, the present study aim to investigate the chemistry of heterocycles incorporating 4,11-diimino-2,9-bis(methylthio)-6-hydroxy-7,11-dihydro-4H,6H-dipyrimido[1,2-a:1',2'-c]pyrimidine-3,10-dicarbonitrile skeletons and their derivatives. The simple and efficient synthesis of amino pyrimidine have been demonstrated by using Michael addition reaction, Michael acceptor ethylecyano acetate and Michael donor guanidine nitrate. The resulting compound 2,6 diamino 4-hydroxy pyrimidine was further reacted with 2-[bis (methylthio)methylene]malononitrile in the presence of catalytic amount of K_2CO_3 in DMF under reflux condition that offered substituted amino pyrimidine. In the compound of amino pyrimidine have replaceable methylthio group, This group are substituted by various nucleophiles such as various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds. The structure and formula of all the synthesized compounds were characterized by spectral data. Some of the synthesized compounds were evaluated for their biological activities. The compounds of this class of heterocycles containing a significant characteristic scaffold and possessing a wide range of biological characteristic.

Keywords: Michael Reaction, 2-[bis(methylthio)methylene]malononitrile, Guanidine Nitrate

1. Introduction

Pyrimidine are the heterocyclic aromatic compound similar to benzene, pyridine containing nitrogen atom at position 1 & 3 of six membered ring. Heterocyclic ring pyrimidine moiety are of great interest because thy constitute an impotence class of natural and non natural product, which many of exhibit useful biological activity and clinical application [6]. Substituted Purines, pyrimidine occur very widely living organisms. Pyrimidines reside in an important position in the medicinal chemistry as it has a number of diverse biological properties. Their related fused heterocycles like pyrimido pyrimidine and its derivatives were of interest as potential bioactive molecules. Pyrimidine derivatives are reported to have diverse pharmacological activities such as anticonvulsant [21], antihypertensive activity [17], analgesic [16], anti-depressive [11], antipyretic [18], anti-inflammatory [14, 15], Chemotherapeutic agents [13], antiviral [10], anti-HIV [25], antimicrobial [26] and anti-tumor activities.

Pyrimidine nucleus is an integral part of biomolecules like DNA and RNA and plays an important role in several biological processes and also has considerable pharmacological uses such as antibiotics, antibacterial [3], cardiovascular as well as agrochemical and veterinary product. By considering all these importance we are synthesized fused pyrimido pyrimidine and its derivatives with simple path.

In presence of pyrimidine base thyamine, cytosin and uracil which are the essential therapeutic application. The literature survey indicated that a wide range of pharmacological activities are exhibited by the compound

encompassing pyrimidine nucleus. In addition to this, various analogy of pyrimidine have been found to posses antibacterial [28], antifungal [12], antioxidant [22, 23], anti-histaminic [24], antiallergy agents [20], antiviral [19], anticancer activities [25] and also act as calcium channel blockers [27].

Heterocyclic compounds are plenteous in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics [4]; hence, they have to drag considerable attention in the synthesis of biologically active molecules [5] and advanced organic chemistry [6]. Also in the group of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial applications [7]. A totally unsaturated membered six-ring containing nitrogen is known as azine [8] or pyridine; with two nitrogen atoms it is known as diazine [9], and with a nitrogen at 1,2-position, it is known as pyridine, at 1,3 position as pyrimidine and at 1,4positionas pyrazine. However, the current review intends to study and deep investigation on the significance of pyrimidine class of antimicrobial agents along with clinical and in vitro applications of pyrimidine derivatives to accessibility the development of more potent as well as effective antimicrobial agents.

In recent years, there has been increasing interest in the synthesis of pyrimidine derivatives, and there are some efficient methods we used to synthesize the pyrimidine ring, allowing access to a large number of fused multifunctionalized pyrimidine derivatives [2].

2. Methods

Melting point were determined in open capillary tubes and are uncorrected. The silica gel F_{254} plates were used for thin layer chromatography (TLC); the spot were examined under UV light and then developed in an iodine vapour. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedure. The spectra were recorded as follows; IR KBR pellets, a Perkin-Elmer RX1 FT-IR spectrophotometer; ^{1}H NMR, $CDCL_3$, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a heraeus CHN-O rapid analyser.

3. Experimental

3.1. Material

All solvents and reagent were obtained commercially and used as recived, guanide nitrate ($CH_6N_4O_3$), Ethyl cyanoacetate ($C_5H_7NO_2$), aromatic amines, aromatic phenols, heteryl amines and active methylene compounds, DMF, K_2CO_3, Carbon disulphide (CS_2), Dimethyl sulphate ($C_2H_6SO_4$), Malononitrile ($C_3H_2N_2$), KOH.

3.2. Scheme

The guanidine nitrate (0.01 mole) in RBF containing DMF solvent with catalytic amount of K_2CO_3 to heat and stir. After refluxed half hour, please drop ethyl cyanoacetate to reflux 4 hour. After reaction complete then diluted with cold water and acidified. The precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol. the resulting compound 2,6 diamino 4-hydroxy pyrimidine was further reacted with 2-[bis (methylthio)methylene] malononitrile in the presence of catalytic amount of K_2CO_3 in DMF refluxed [1] for 4hour that offered 9-Hydroxy-4,8-diimino-2,6-bis-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile (1). The compound (1) confirmed by IR, 1H and C13 NMR and MS analytical data.

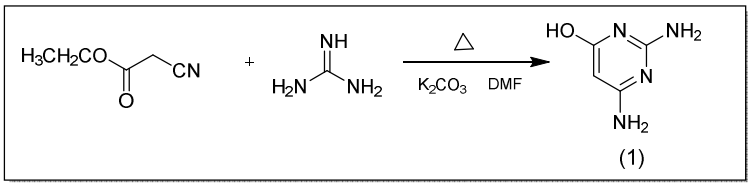

Figure 1. *Synthesis of 2,4 diamino 4-hydroxy pyrimidine.*

After purification and characterization, the obtained compound 2,6 diamino 4-hydroxy pyrimidine (1) was converted into 4,11-diimino-2,9-bis(methylthio)-6-hydroxy-7,11-dihydro-4H,6H-dipyrimido[1,2-a:1',2'-c]pyrimidine-3,10-dicarbonitrile by treating it with 2-(bis (methylthio) methylene) malononitrle in the presence of catalytic amount of K_2CO_3. The obtained structure (2).

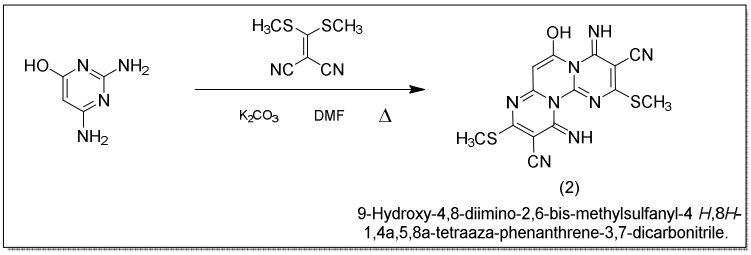

Figure 2. *Synthesis of Nucleus.*

3.3. Synthesis of Derivatives

In the compound (2) there is a replaceable methylthio group hence acts as electrophilic species. A mixture of (2) and independently, various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds in DMF (10 ml) and anhydrous potassium carbonate (10 mg) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized using ethyl alcohol. The compounds confirmed by IR, 1H and C13 NMR and MS analytical data.

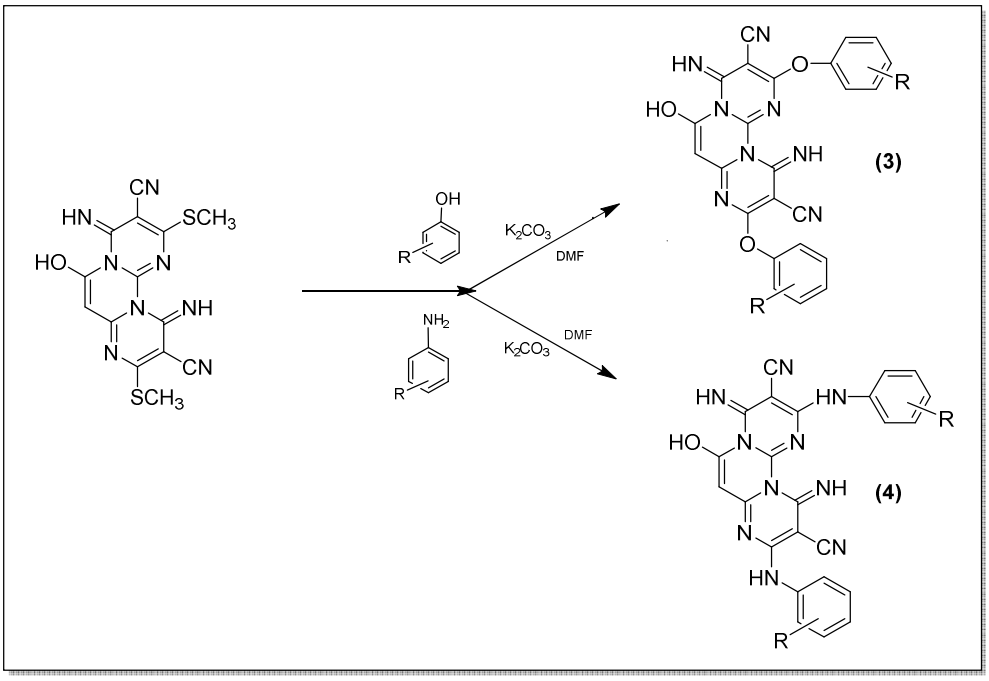

Figure 3. *Synthesis of Derivatives (3), (4).*

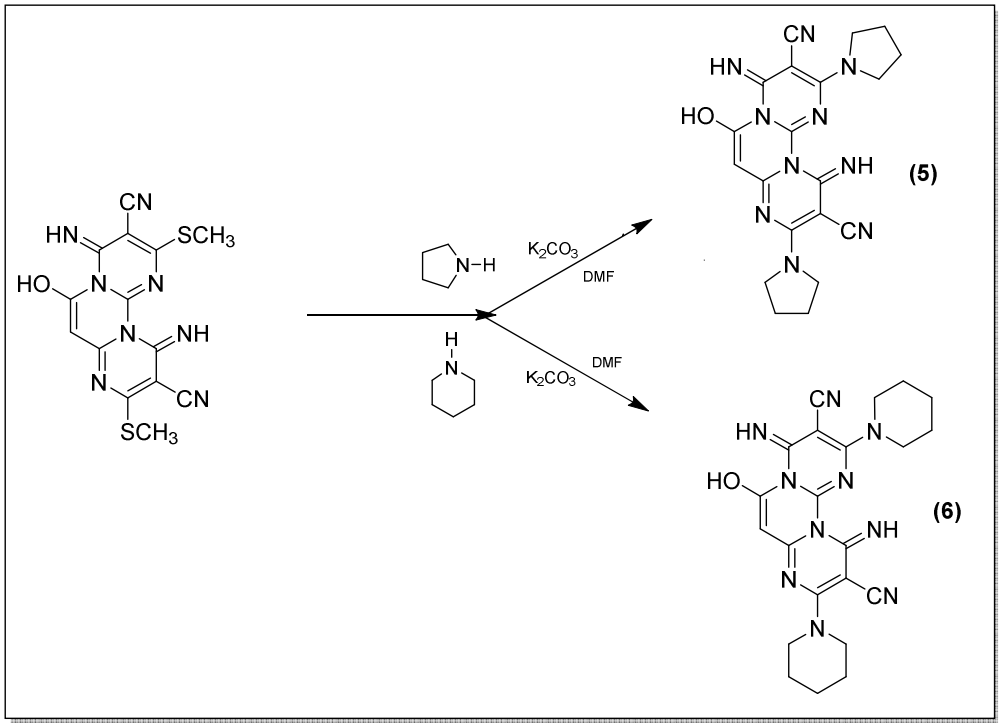

Figure 4. *Synthesis of Derivatives (5),(6).*

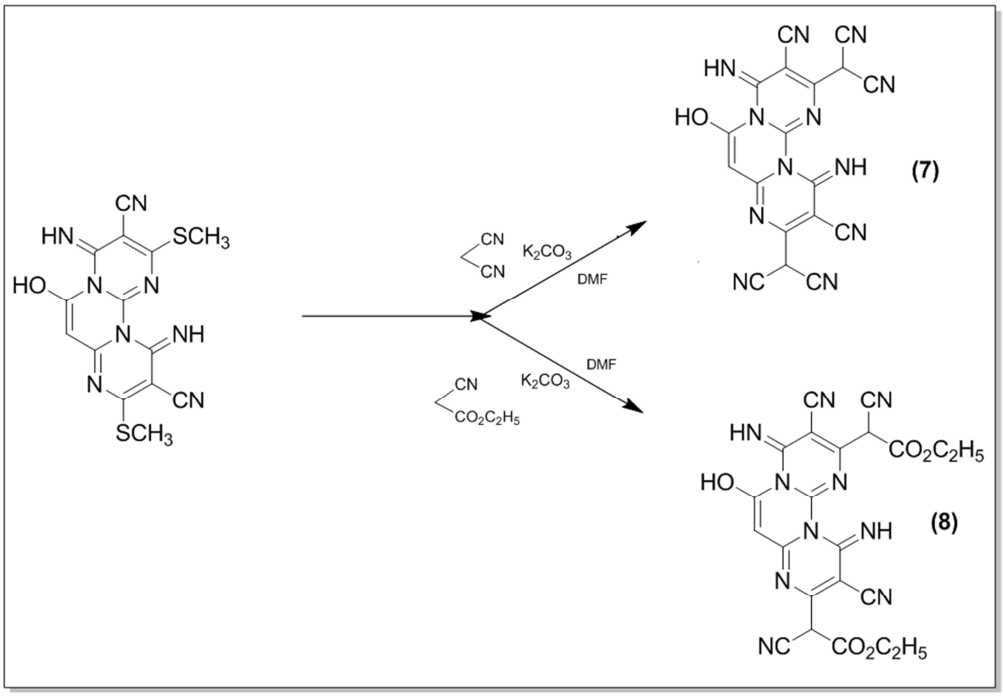

Figure 5. *Synthesis of Derivatives (7),(8).*

4. Conclusion

In summary, we have synthesized novel amino pyrimidine in a family of nitrogen containing compounds, The fused heterocyclic 9-Hydroxy-4,8-diimino-2,6-bis-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile and their derivatives by using simple and efficient chemistry. This synthesized compounds act as an electrophilic species and reacting with various nucleophiles such as various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds. In compounds cyano and thiomethyl groups are at adjacent position it also undergo cyclization to give polycyclic heterocyclic compound.

1) 9-Hydroxy-4,8-diimino-2,6-bis-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3340, 3430, 1580, 2250.

^{1}H NMR: δ 2.50 (S, 3H, SCH_3), δ 9.36 (S, 1H, = NH), δ 6.20 (S, 1H, =CH), δ 9.32 (S, 1H, =NH), δ 2.52 (S, 3H, SCH_3), δ 7.68 (S, 1H, OH).

ESI-MS: 370.41.

Anal. Calcd for: $C_{14}H_{10}N_8S_2O$.

Mol. Formula: $C_{14}H_{10}N_8S_2O$.

Mol. Wt. 370.41.

2) 9-Hydroxy-4,8-diimino-2,6-phenoxy-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3345, 3420, 1585, 2230.

^{1}H NMR: δ 9.30 (s, 1H, =NH), δ 5.22 (s, 1H, =CH), δ 9.25, (s, 1H, =NH), δ 7.40 (s, 1H, OH), δ 6.73 (dd, 2H, Ar-H), δ 7.04 (dd, 2H, Ar-H).

ESI-MS: 460.40.

Anal. Calcd for: $C_{24}H_{12}N_8O_3$.

Mol. Formula: $C_{24}H_{12}N_8O_3$.

Mol. Wt. 460.40.

3) 9-Hydroxy-4,8-diimino-2,6-phenylamino-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3360, 3425, 1570, 2240.

^{1}H NMR: δ 9.38 (s, 1H, =NH), δ 5.3 (s, 1H, =CH), δ 9.35, (s, 1H, =NH), δ 7.40 (s, 1H, OH), δ 6.46 (dd, 2H, Ar-H), δ 7.01 (dd, 2H, Ar-H), δ 3.8 (s, 1H, NH).

ESI-MS: 458.43.

Anal. Calcd for: $C_{24}H_{14}N_{10}O$.

Mol. Formula: $C_{24}H_{14}N_{10}O$.

Mol. Wt. 458.43.

4) 9-Hydroxy-4,8-diimino-6-methylsulfanyl-2-pyrrolidin-1-yl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3335, 3445, 1550, 2260.

^{1}H NMR: δ 9.34 (s, 1H, =NH), δ 5.4 (s, 1H, =CH), δ 9.45, (s, 1H, =NH), δ 7.60 (s, 1H, OH), δ 2.4 (t, 4H, C-H), δ 1.59 (m, 4H, C-H), δ 1.5 (m, 2H, CH).

ESI-MS: 416.43.

Anal. Calcd for: $C_{20}H_{20}N_{10}O$.

Mol. Formula: $C_{20}H_{20}N_{10}O$.

Mol. Wt. 416.43.

5) 9-Hydroxy-4,8-diimino-6-methylsulfanyl-2-piperidin-1-yl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3345, 3455, 1540, 2250.

^{1}H NMR: δ 9.34 (s, 1H, =NH), δ 5.4 (s, 1H, =CH), δ 9.45 (s, 1H, =NH), δ 11.40 (s, 1H, OH), δ 2.7 (t, 4H, C-H), δ 1.5 (m, 6H, C-H).

ESI-MS: 444.49.

Anal. Calcd for: $C_{22}H_{24}N_{10}O$.

Mol. Formula: $C_{22}H_{24}N_{10}O$.

Mol. Wt. 444.49.

6) 2-Dicyanomethyl-9-hydroxy-4,8-diimino-6-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7-dicarbonitrile.

IR: 3365, 3450, 1575, 2240.

^{1}H NMR: δ 9.34 (s, 1H, =NH), δ 5.4 (s, 1H, =CH), δ 9.45 (s, 1H, =NH), δ 11.40 (s, 1H, OH), δ 4.18 (s, 1H, C-H).

ESI-MS: 378.30.

Anal. Calcd for: $C_{18}H_6N_{12}O$.

Mol. Formula: $C_{18}H_6N_{12}O$.

Mol. Wt. 378.30.

7) Cyano-(3,7-dicyano-9-hydroxy-4,8-diimino-6-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthren-2-yl)-acetic acid ethyl ester.

IR: 3340, 3460, 1565, 2245.

^{1}H NMR: δ 9.24 (s, 1H, =NH), δ 5.43 (s, 1H, =CH), δ 9.35 (s, 1H, =NH), δ 7.8 (s, 1H, OH), δ 4.01 (s, 1H, C-H), δ 4.12 (q, 2H, C-H), 1.30 (t, 3H, C-H).

ESI-MS: 500.42.

Anal. Calcd for: $C_{22}H_{16}N_{10}O_5$.

Mol. Formula: $C_{22}H_{16}N_{10}O_5$.

Mol. Wt. 500.42.

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