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Studies on acetylpyrimidine: A facil one–pot synthesis of condensed pyrimidines

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ABSTRACT

Cyclo addition of benzal acetophenone to mercaptopyrimidine **(1)** afforded thiopyranopyrimidine **(5)**. Ethylglycinate **(7a)** reacted with chloropyrimidine **(6)** to produce deazapurine **(10)** while ethylphenylglycinate **(7b,c)** yielded pyrrolopyrimidine **(9a,b)**. The synthesis of pyrimidodiazpen **(13)** was achieved from the condensation reaction between compound **(6)** and hydrazine derivative **(11)**. The synthesis of pyrimidoquinoline **(16)**, pyridopyrimidine **(21)**, **(24)** was also described.

KEYWORDS

Mercaptopyrimidine;
Chloropyrimidine;
Thiopyranopyrimidine;
Quinolinopyrimidine;
Pyrimidoazapene;
Pyridopyrimidine.

INTRODUCTION

It was well known that pyrimidine derivatives were of great biological interest, especially as antimicrobial[1-4], Anti-HIV[5,6], anti-inflammatory[7,8] and antitumor agents[9-18]. Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarly due to very wide spectrum of biological activities. This is evident in particular from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles such as purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrolopyrimidines. Many simple fused pyrimidines such as purines and pteridines were biologically active by themselves[19,20], or were essential components of very important naturally occurring substances (i.e., nucleic acids). Some pteridine derivatives were also used as anti-leukemic drugs[21], or potassium conserving diuretics[22]. In addition, several quinazoline alkaloids exhibit hypnotic[23,24], bronchldilatory[25], and antimalarial[26,27] activity. 2-Thiouracils and 6-aryl-2- thiouracils were well known for their antimicrobial, anticancer and antiviral activities[28-30]. Although chloro/ mercapto pyrimidines were readily obtainable via efficient synthetic routes[31,32]. The utility of these versatile pyrimidines for the construction of azino and diazapenopyrimidine has received very limited attention[33-35]. In conjugation of our effort directed toward the synthetic potential of chloropyrimidines[36]. The chemistry of the 4-(mercapto\chloro)-5-acetylpyrimidine was here reported.

RESULTS AND DISCUSSION

Cycloaddition reaction of mercapto function to activated ethenylic compound were well known and documented[37], they have been widely used in the synthesis of various heterocyclic systems.

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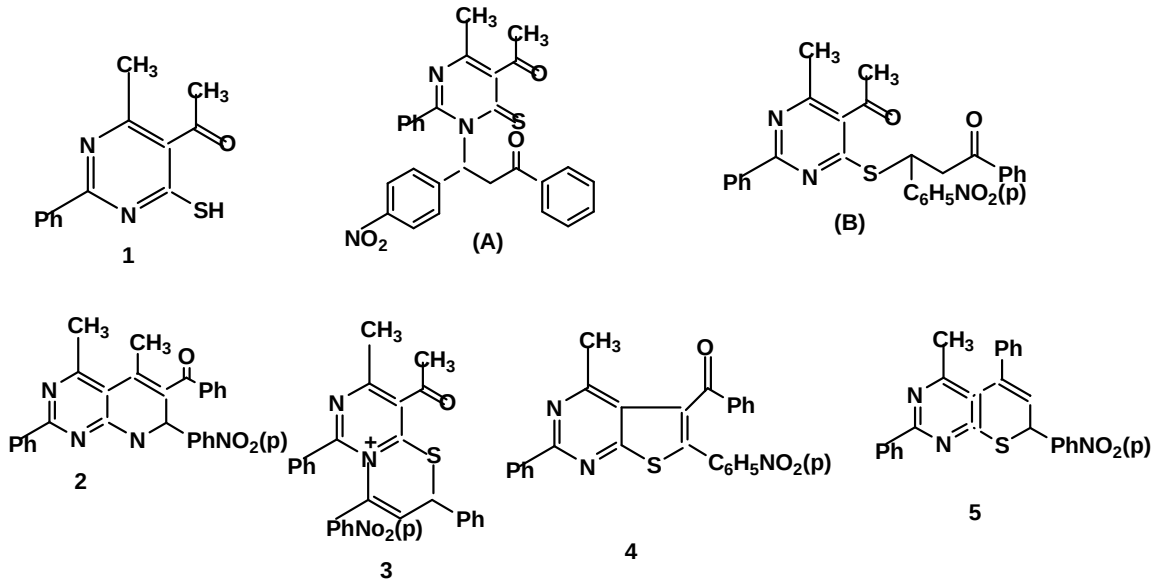
The starting material, pyrimidinthione **(1)** was prepared according to literature procedure by reaction of benzoylisothiocynate and enaminone[38]. In principle, both nucleophilic nitrogen and thiol of pyrimidinthione **(1)** can take part in the cycloaddition reaction with activated double bond to form N-adduct **(A)** or S-adduct **(B)**. In our preliminary report we have shown that S-adduct of compound **(1)** is formed upon cyanoethylation reaction.

Thiopyranopyrimidine **(5)** was synthesized by one pot of base catalyzed two components reaction of mercaptopyrimidine with Michael acceptor p-nitrobenzalacetophenone. Based the absence of absorption of carbonyl, the expected products **(2)**, **(3)** and **(4)** were ruled out (Scheme 1).

A reasonable mechanism for the construction of thiopyranopyrimidine derivative **(5)** would involve the initial addition of pyrimidinthiol **(1)** to benzalacetophenone derivative forming Michael adduct **(B)**, then **(B)** into the reactive species **(C)**, which undergoes 1,3- acetyl shift, with the formation of ester **(D)**. Finally, the elimination of acetic acid, lead to the formation of the target thiopyranopyrimidine derivative **(5)** (Scheme 2). The ^{1}H NMR spectrum of thiopyranopyrimidine **(5)** showed multiplet at δ (6.6 – 8.6) ppm for methinyl and aromatic protons.



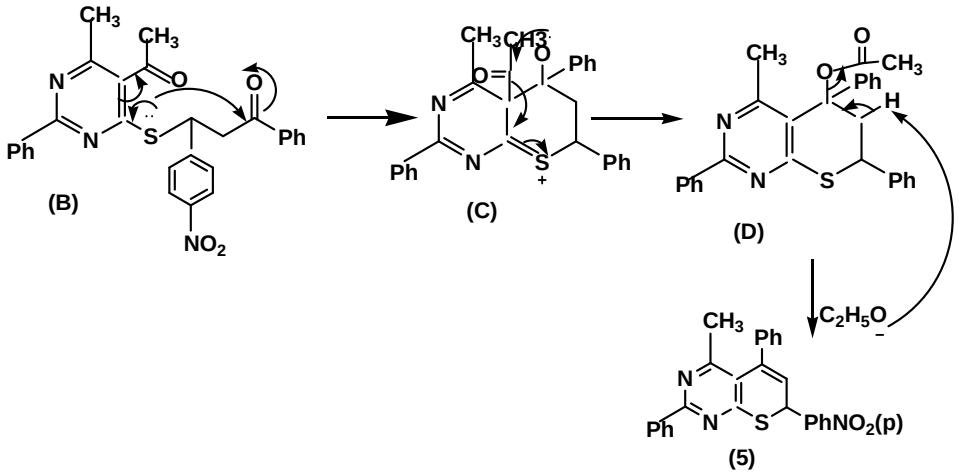
Scheme 1

To examine further scope of the methodology, the bifunctional compound **(6)** was employed to subject with N-arylglycinate **(7a-c)**. The results indicated that aryl group of glycinate bearing either satirically hindered group at ortho position (2-ethylphenyl) or electron acceptor group (3-chlorophenyl), were suitable for the synthesis of compound **(9a,b)**. The IR spectrum of compound **(9a, b)** showed a strong absorption at 1653 and 1647 cm^{-1} due to the carboxylic carbonyl. The ^{1}H NMR spectrum signal at δ 12.9 ppm for the carboxylic proton.

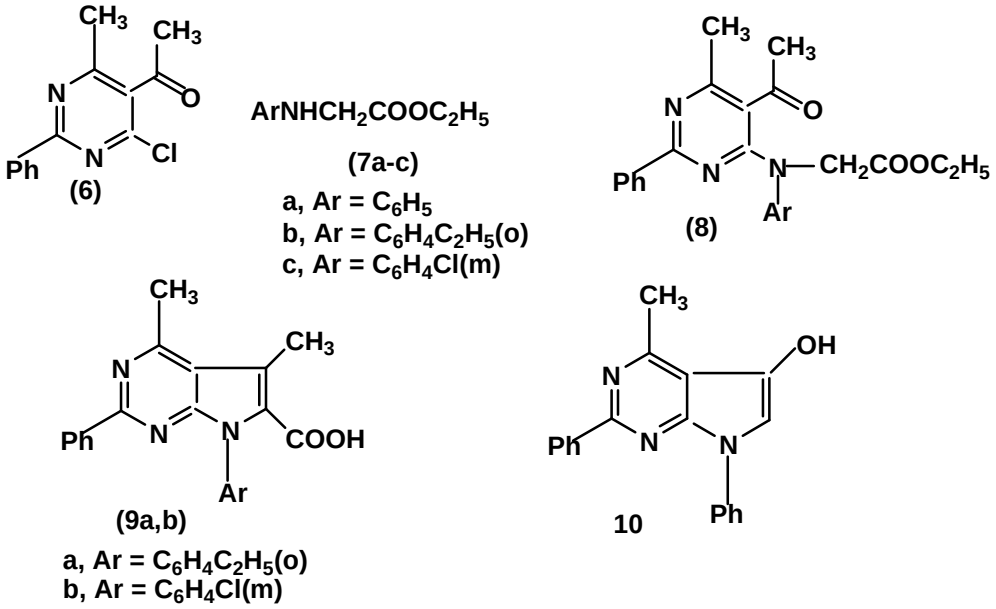
A cyclization reaction takes place with compound **(6)** in the case of phenylglycinate resulting in the formation of pyrrolopyrimidine **(10)** (scheme 3). Deazapurine **(10)** was characterized by IR and ^{1}H NMR spectra. Pyrrolopyrimidine **(10)** show the characteristic signal of pyrrole OH at δ 10.6 ppm. The IR spectra of compound **(10)** displayed the characteristic absorption band for OH in the region 3240 – 3500 cm^{-1}.

Base catalyzed substitution of the chloro group of compound **(6)** with thiocarbamate **(11a)** provided pyrimidodiazapen **(13)**, presumply via the formation of non isolable hydrazine derivative **(12)** followed by intramolecular nucleophilic heterocyclization via loss of H_2S (scheme 4). This construction was potentiated by the presence of mercapto proton at δ 11.4 ppm. IR spectrum for compound **(13)** contained band at 1680 cm^{-1} due to the carbonyl group.

Displacement of chloro group of chloropyrimidine **(6)** with thiocarbamate **(11b)** furnished quinolinopyrimidine **(16)**. A reasonable mechanism for the formation of **(16)** was proposed in (scheme 5). The formation of **(16)** was expected to proceed via initial



Scheme 2

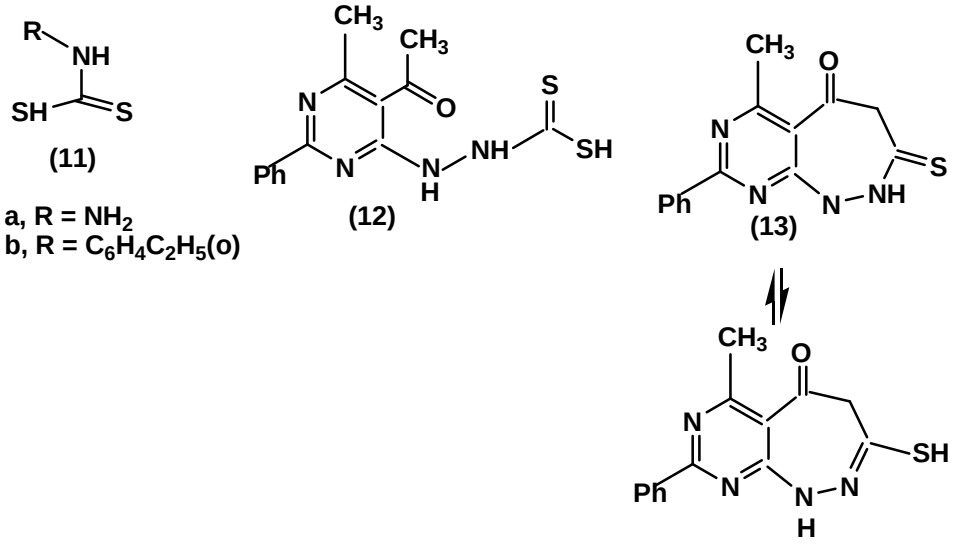


Scheme 3

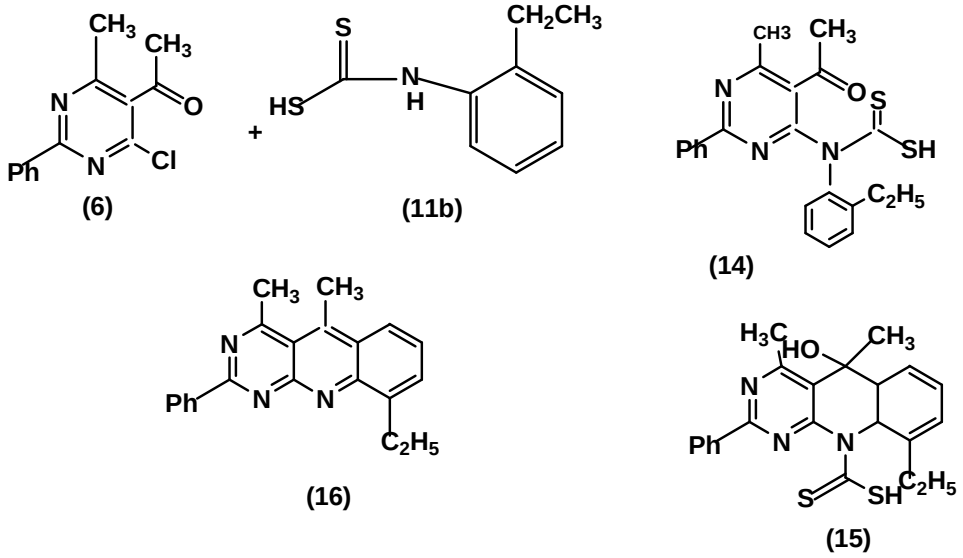
reaction of **(11b)** and bifunctional compound **(6)** to afford acetylheterocyclic amine **(14)**, and then the intramolecular cyclization would provide non isolable intermediate **(15)**, which sequenttlial H_2O and CS_2 elimination to afforded the final product ?? !!!. The structure of this product was proved by its spectroscopic data thus, IR spectrum of compound **(16)** lack the carbonyl and NH function

4-Amino-5-acetylpyrimidine **(17)** was prepared by amonolysis of 4-chloropyrimidine **(6)**[39]. In an attempted to prepare pyrimidopyrimidine **(19)** by refluxing of compound **(17)** with ammonium isothiocynate in dioxin the starting material was recovered completely unchanged. In contrast when the reaction was conducted under thermal process pyridopyrimidine **(21)** is obtained and non of thiourea derivative **(18)** or its cyclized product **(19)** (is formed may be due to the deactivation of (-NH_2) by strongly acceptor nature of pyrimidine) (scheme 6)

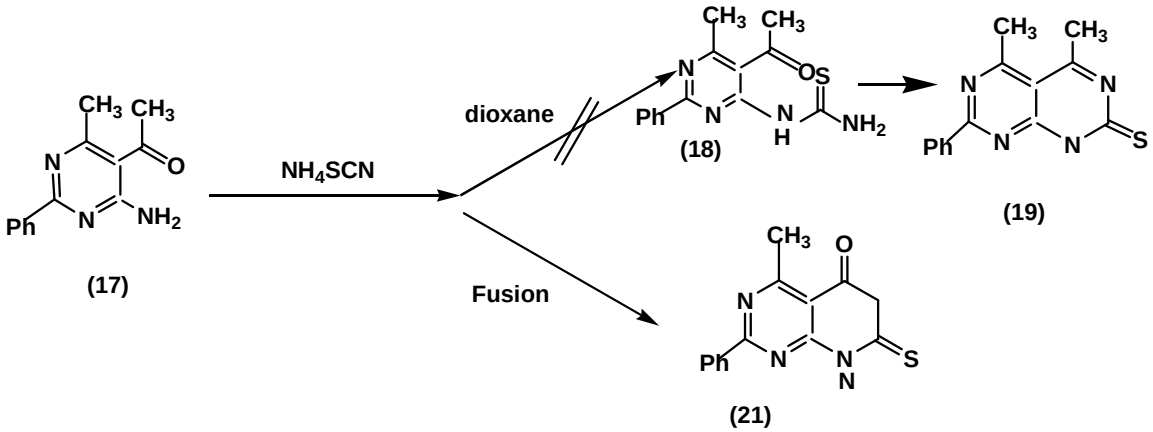
The transformation of 4-amino-5-acetylpyrimidine **(17)** into pyridopyrimidine **(21)** probably proceeds through the intermediacy of **(20)** through the addition of enolic form of **(17)** to isothiocynate and subsequent heterocyclization by the loss of NH_3 molecule. The ^1H NMR spectrum was consistent with the structure of the new compound **(21)**, which displayed a singlet for the proton at positions at δ 2.5, 4.1 and 7.2 ppm in addition to aromatic proton at δ (7.5 – 8.2) ppm. The structure was also confirmed by the presence of C=S and C=O at 1373 and 1672 respectively.



Scheme 4

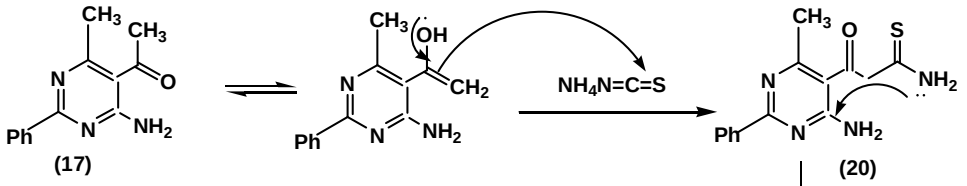


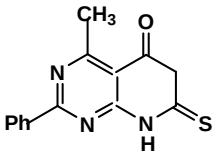
Scheme 5



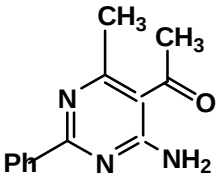
Scheme 6

Compounds having formula **(24a,b)** was obtained via condensation of 4-amino-5-acetylpyrimidine **(17)**

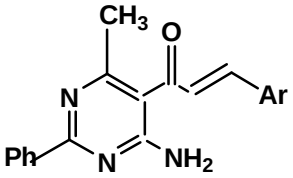




(21)



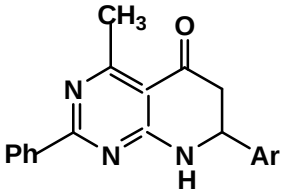
(17)



(22a,b)

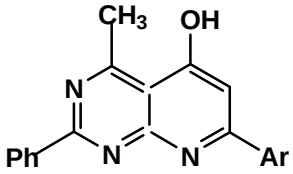
a Ar=C_6H_5

b Ar=$C_6H_4NO_2$(m)



(23)

Ar=$C_6H_4NO_2$(m)



(24)

Ar=$C_6H_4NO_2$(m)

with aldehyde in basic medium [ethoxide or triethylamine] thus, heterocyclization of compound **(17)** with m-nitrobenzaldehyde afforded pyridopyrimidine **(24a,b)**. Presumably via the initial formation of cinnamoylptrimidine **(22)** followed by intramolecular cycloaddition and subsequent aromatization ^{1}H NMR of the adduct **(24)** showed the presence of hydroxyl proton at δ 8.1 ppm, also gave band at 3077 cm^{-1} in its IR spectrum.

While the reaction of benzaldehyde with 4- amino-5-acetylpyrimidine produced the cinnamoyl derivative **(22a)**. Cinnamoylpyrimidine **(22a)** was well characterized by IR and 1H NMR spectra. Schalcone **(22a)** showed signal for ethylenic and aromatic proton at δ (6.02-8.5) ppm. The IR spectrum of cinnamoylpyrimidine **(22a)** displayed at 1674 cm^{-1} for ketonic carbonyl.

EXPERIMENTAL SECTION

General procedures

All melting points were uncorrected and were recorded on Büchi 510 apparatus. IR spectra were recorded as KBr disks on a Perkin- Elmer 383- Spectrometer and FTIR spectrometer Nicollet, impact 400. ^{1}H NMR was obtained a Bruker Ac 200f and Ac 250, DRX400instrument at room temperature using TMS as internal standard. Micro analysis were carried out at micro analytical center, Cairo University, Egypt and Friedrich – Schiller University, Jena, Germany.

1- 5-Acetyl-4-methyl-2-phenyl-6-thiopyrimidine (1)

Was prepared according to the reported procedure[38].

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2- P-nitrobenzal acetophenone

Was prepared according to the reported procedure[40].

3- 6-p-(Nitrophenyl)-3-phenyl-[2,3-d]-thiopyranopyrmidine (5)

An equimolar amounts of pyrimidine **(1)** and p-Nitrobenzalacetophenone was refluxed in ethoxide\ethanol for five hours then neutralized with hydrochloric acid. The solid obtained upon filtration and crystallized from ethanol gave 90% of **(5)** as brown solid: mp 190 °C. Anal. Calcd. For $C_{32}H_{59}N_2S$: C 76.28, H 11.80, N 5.56. Found: C 76.20, H 11.78, N 5.5. ^{1}H NMR spectrum, δ, ppm: 2.502(s, 3H, CH_3) and 6.6 - 8.6 (m, 17H, ArH's) and methinyl)

4- N-arylglycinate (7a-c)

Was prepared according to the reported procedure[41].

5- N-(o-ethylphenyl)-4-methyl-5-carboxy-[2,3-d]pyrrolopyrimidine (9b)

An equimolar amounts of chloropyrimidine **(6)** and N-arylglycinate **(7b)** was refluxed in ethanol in the presence of TEA for five hours. The solid obtained upon concentration, dilution with water (20 ml), acidification with acetic acid and crystallized from methanol gave 80% of **(9b)** as brown slolid: mp 210 °C. Anal. Calcd. For $C_{23}H_{21}N_3O_2$: C 71.04, H 11.45, N 9.94. Found: C 71.01, H 11.40, N 9.91. ^{1}H NMR spectrum, δ, ppm: 1.9(s, 3H, CH_3), 2.5(s, 3H, CH_3), 7.32-8.45(m, 9H, ArH's) and 12.9(s, 1H, COOH). IR spectrum (υmax, cm^{-1}): 1546 (C=N), two strong peaks at 776, 699 (meta di-substituted benzene), 1653 (C=O of α,β- un saturated acid).

6-N-(m-chlorophenyl)- 4-methyl-5-carboxy-[2,3-d]pyrrolopyrimidine (9c)

An equimolar amounts of chloropyrimidine **(6)** and N-arylglycinate **(7c)** was refluxed in ethanol in the presence of TEA for five hours. The solid obtained upon concentration, dilution with water (20 ml), acidification with acetic acid and crystallized from methanol gave 70% of **(9c)** as brown solid: mp 155 °C. Anal. Calcd. For $C_{21}H_{16}N_2O_2Cl$: C 64.91, H 10.46, N 9.08. Found: C 64.80, H 10.40, N 8.98. ^{1}H NMR spectrum, δ, ppm: 2.501(s, 3H, CH_3), 7.5-8.1(m, 9H, ArH's) and 13(s, 1H, COOH). IR spectrum (υmax, cm^{-1}): 1564(C=N), two strong peaks at 777, 696 (meta di-substituted benzene) and 1647 (C=O of α,β- un saturated acid).

7- N-phenyl- 4-hydroxy-[2,3d]pyrrolopyrimidine (10)

An equimolar amounts of chloropyrimidine **(6)** and N-arylglycinate **(7a)** was refluxed in ethanol in the presence of TEA for five hours. The solid obtained upon concentration, dilution with water (20 ml), acidification with acetic acid and crystallized from methanol gave 70% of **(10)** as brown solid 10: mp 215 °C. Anal. Calcd. For $C_{19}H_{15}N_3O$ C 76.17, H 11.96, N 8.6. Found C 76.12, H 11.90, N 8.1. ^{1}H NMR spectrum, δ, ppm: 2.5 (s, 3H, CH_3), 7-8.4 (m, 10H, ArH's) and 10.6(s, 1H, OH). IR spectrum (υmax, cm^{-1}): 1654(C=N), 3240-3500(OH).

8- thiocarbamate (11a,b)

Was prepared according to the reported procedure[42].

9- 4-Methyl-7-thio-[2,3-d]pyrimido-1-thia-5,7-diazap-4-ene (13)

An equimolar amounts of chloropyrimidine **(6)** and thiocarbamate **(11a)** was refluxed in 20 ml methanol in the presence of sodium carbonate for five hours. The solid obtained upon dilotion with water and acidification with hydrochloric acid was collected and crystallized from methanol gave 70% of **(13)** as brown solid: mp 122 °C. Anal. Calcd. For $C_{14}H_{12}N_3S_2$: C 62.97, H 10.79, N 12.24. Found C 62.90, H 10.70, N 12.20. ^{1}H NMR spectrum, δ, ppm: 2.5(s, 3H, CH_3), 7.1-8.5(m, 5H, ArH's) and 11.4(s, 1H, SH). IR spectrum (υmax, cm^{-1}): 1622 (C=N) and 1680 (C=O).

10- N-(o-ethyl)-4-methenyl-6-thiopyrimido-1,5-thiazine (16)

A solution of chloropyrimidine **(6)** (0.01 mole) and thiocarbamate **(11b)** (0.01 mole) in methanol (60 ml) was heated under reflux for five hours, the solid separated upon cooling were crystalized from methanol and gave 60% of **(16)** as brown solid: mp 250 °C. Anal. Calcd. For $C_{22}H_{14}N_3S_2$: C 59.32, H 9.31, N 9.02. Found C 59.30, H 9.30, N 8.99. ^{1}H NMR spectrum, δ, ppm: 1.21 (t, 3H, CH_3), 2.509(s, 3H, CH_3), 2.497

(s, 3H, CH_3), 2.601- 3.303(q, 2H, CH_2) and 7.006-8.182(m, 9H, ArH's) andIR spectrum (υmax, cm^{-1}): 1636 (C=N) and 753 (O- disubstituted aromatic ring).

11- 4-Amino-5-acetylpyrimidine (17)

Was prepared according to the reported procedure[39].

12- 4-Oxo-6-thio-[2,3-d]-pyridopyrimidine (21)

A mixture of aminopyrimidine **(17)** (0.01 mole) and ammoniumthicynate was fused for half hour then add acetic acid and pour on water. The solid obtained upon filtration and crystallized from methanol gave 70% of **(21)** as brown solid: mp 200 °C. Anal. Calcd. For $C_{14}H_{11}N_3OS$: C 66.79, H 10.45, N 10.62. Found C 66.70, H 10.42, N 10.60. ^1H NMR spectrum, δ, ppm: 2.506(s, 3H, CH_3), 4.129(s, 2H, CH_2), 7.288(s, 1H, NH) and 7.567-8.470(m, 5H, ArH's). IR spectrum (υmax, cm^{-1}): 3464 (NH), 1373 (C=S), 1672 (C=O) and 1563 (C=N).

13- 4-amino-6-methylcinnamoylpyrimidine (22a)

A mixture of aminopyrimidine **(17)** (0.01 mole) and benzaldehyde (0.01 mole) was refluxed in ethoxide\ethanol then neutralized with hydrochloric acid. The solid obtained upon filtration and crystallized from methanol gave 80% of **(22a)** as brown solid: mp 210 °C. Anal. Calcd. For $C_{19}H_{17}N_3O$: C 67.18, H 12.53, N 8.7. Found C 67.15, H 12.4, N 8.4. ^1H NMR spectrum, δ, ppm: 2.172(s, 3H, CH_3), 6.02(s, 1H, CH ethylenic) and 6.025-8.579(m, 12H, ArH's+NH_2). IR spectrum (υmax, cm^{-1}): 1674 (C=O).

14- 4-Hydroxy-6-(m-nitrophenyl)pyridopyrimidine (24)

A mixture of aminopyrimidine **(17)** (0.01 mole) and m-nitrobenzaldehyde was refluxed in methanol for four hour in the presence of TEA. The solid obtained upon concentration, dilution with water (20 ml), acidification with acetic acid and crystallized from methanol gave 90% of **(24)** as brown solid: mp 256 °C. Anal. Calcd. For $C_{20}H_{14}N_4O_3$. C 36.48, H 5.20, N 4.25. Found C 36.44, H 5.10, N 4.20. ^1H NMR spectrum, δ, ppm: 2.543(s, 3H, CH_3) and 7.626-8.174(m, 10H,ArH's+OH). IR spectrum (υmax, cm^{-1}): 3077 (OH), 1647 (C=N) and two strong peaks at 772, 697 (due to meta di-substituted aromatic ring).

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