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Synthesis of new nitrogen bases derived from the nucleic acid nitrogen base uracil in targeting the modification of the nucleic acid systems.

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ABSTRACT

2-Hydrazino derivative 3 was refluxed with aromatic aldehydes (1:1, molar ratio) in presence of ethanol afforded Schiff's bases 4a-c. Reaction of 4-chlorobenzaldehyde with 2-hydrazino derivative 3 (1:2, molar ratio) produced Schiff's base 6. On other hand, cyclization of compound 4b, using bromine (1:1) in glacial acetic acid, the 5-bromo- open structure 7 was obtained. The cyclized structure 8 was formed on reacting 4b with bromine in (1:2, molar ratio). 7-Amino-3-thioxo-2,3-dihydro-1H,5H-s-triazolo[4,3-a]primidin-5-one (12) was obtained upon treatment the potassium salt of derivative 3 with carbon disulphide. On stirring chloroacetyl chloride with 2-hydrazino derivative 3 in cold anhydrous dioxane, compound 8-amino-1,2,3,4-tetrahydro-6H-pyrimido[2,1-c]-as-triazine-3,6-dione (14) was produced. The reaction of 3 with either 2,4-pentanedione or 3-chloro-2,4-pentanedione furnish the class compound 16a,b. Heating under reflux compound 3 with ethyl acetoacetate furnish the cyclized product 17.

Keywords: amino uracil, hydrazine uracil, nitrogen bases, nucleic acid modification.

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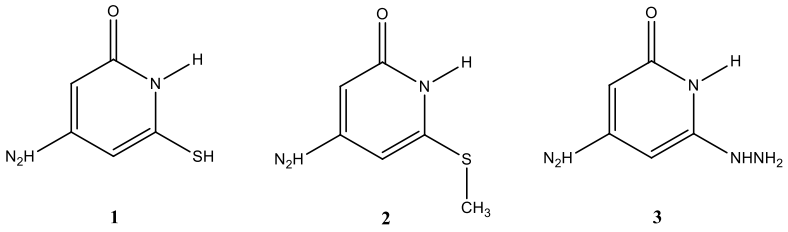
INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is not only threatening the human life style but only considered as a main cause of mortality of millions of human lives [1]. That fact prompts thousands of scientists in a broad range of specialties to be devoted to compose new drugs to have effect against the HIV [2-4]. One of the ways to do so was by designing and synthesis of new nucleoside analogues. The modification of the nucleic acid was based on either modification of the carbohydrate [5] or the nitrogen base [6] or both of the 2 parameters composing the nucleic acid system.

Our work concentrated on modification of the nitrogen base Uracil derivative through the derivative 6-amino-2-thiouracil **1**. We picked this particular derivative and subjected it to modification because it is chemically and biologically active compound. Its derivatives had wide spectrum of application as used as antithrombotic[7], antimicrobial, anti-inflammatory[8], antiviral[9], antidotal, anticancer agents[10] and potent inhibitors of interleukin-8-induced neutrophil chemotaxis[11]. Also, they are utilized in other medicinal purposes[12] and in photography as stabilizers in photographic emulsions[13].

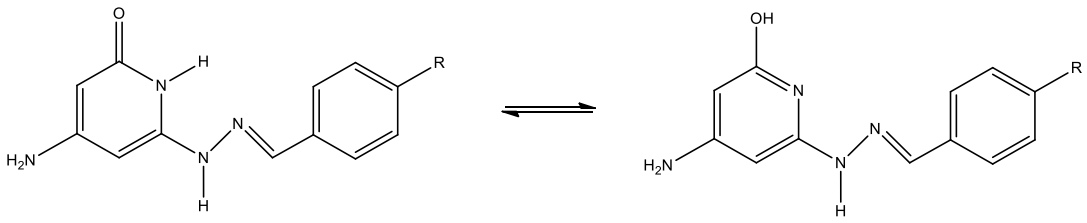
In our last report we indicate a facile and convenient method to transform compound **1** to our precursor **3** through the derivative **2**[14] .



1 **2** **3**

DISCUSSION

Treatment of the 2-hydrazino derivative **3** with an equimolar amount of aromatic aldehyde, in refluxing ethanol condenses with the hydrazine group and not with the amino group to yield the Schiff's bases **4**. The ^{1}H-NMR data suggests that the resultant compound favour the existence in the enol-form **5** rather than the keto-form **4** as the pyrimidine ring is stabilized with the ring aromaticity, as the hydrogen atom displayed as phenolic proton with 100% conversion for some derivatives like 5_a. While some derivatives displays that proton as enol-form(OH) in liquid state only and in solid state displays the equilibrium keto-form(IR) and enol-form, other derivatives displays that proton in both keto-enol states as only in enolate-form (*see Experimental*)



4 **5**

R	4	5
a	-C_6H_4-OCH_3-*P*	-C_6H_4-OCH_3-*P*
b	-C_6H_4-NCH_2-*P*	-C_6H_4-NCH_2-*P*
c	-Ph	-Ph

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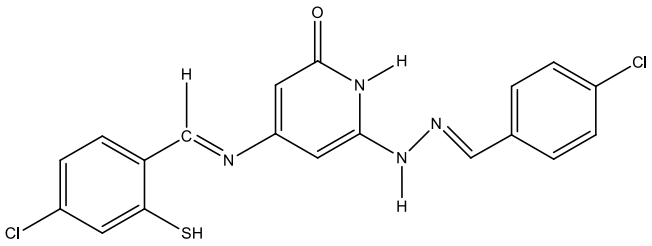
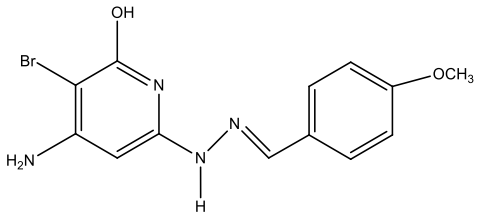
When taking the aromatic aldehyde in dual ratio to the derivative **3,** the condensation product employ the second mole of the aldehyde with the amino group at position 6 to furnish compound **6**. To the contrary of compound **5** compound **6** prefer the existence in the keto-form even in the liquid state. This assumption based on the ^{1}HNMR proves the existence of the NH group.



6

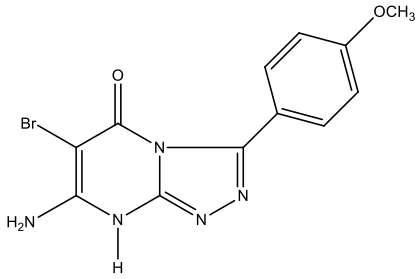
The propused structures of both compound 5 and 6 match to both elemental and spectral data (*experimental).*

Cyclization compound **4b**, by bromination with employing molecular ratio was a total failure with regard to producing a cyclized form and the reaction proceed in the direction of brominating compound **4b** at position 5 to afford compound **7**. This finding was based on ^{1}HNMR spectrum (DMSO-d_6), the only noticeable difference from the chart of compound **4b** is the disappearance of the methine proton of the pyrimidine ring.



7

So, cyclization of compound **4b** could be achieved by employed the same reaction conditions used for the last reaction except using bromine in dual ratio to afford the linear structure **8** rather than the isomeric angular structure **9**



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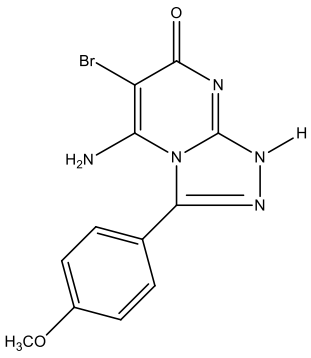

9

Structure **8** was established for the reaction product based on:

1. Bromination of compound 10 affords compound **11**[15].
2. In IR spectrum analysis of **8** shows positive absorption at 1698 cm^{-1} (CO). Moreover, in 1H-NMR the disappearance of the enol-form at around 11 ppm for that proton proves that this proton does not exist anymore. The carbonyl absorption band suffered a high frequency shift indicating the formation

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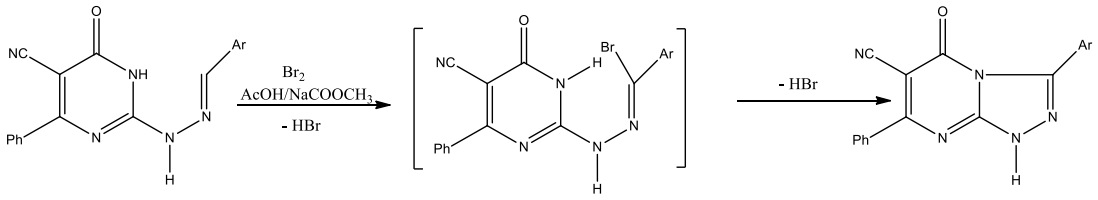
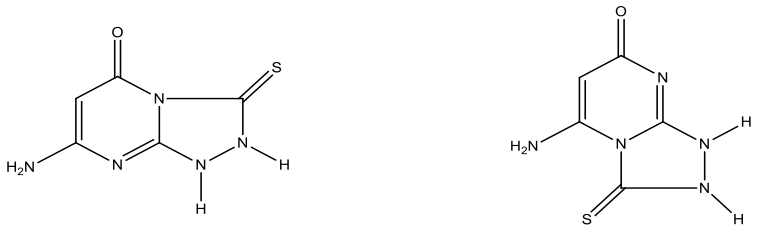
or tertiary amide compound **8**. This shift elucidates structure **8** of the isomeric angular structure **9.** That could be understood from the fact that the a higher absorption frequency is assigned to a carbonyl group attached to a tertiary nitrogen atom than that assigned to a secondary nitrogen[16].

3. The ^{1}HNMR spectrum (DMSO-d_6) of compound **8** shows the absence of the pyrimidine methine proton that was brominated.



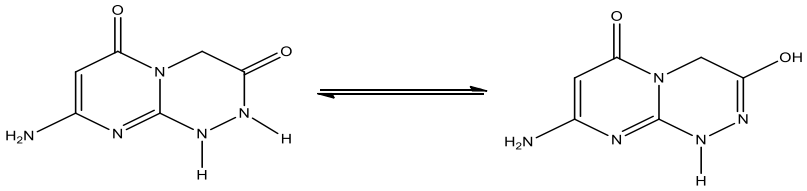
!0 11

Compound **12** was generated from the 2-hydrazino derivative **3** by the action of carbon disulphide. Again the reaction product favours the linear fused structure **12** over the angular isomeric structure **13** on the same basis like compound **8** {***see*** E*xperimental}*

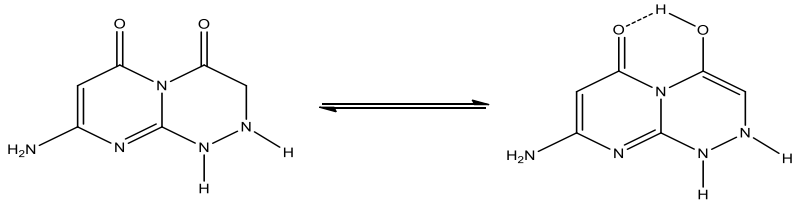


12 13

Compound **14** was formed by the action of chloroacetyl chloride on compound **3** and not the isomeric structure **15**. The ^{1}H-NMR suggested the existence of the keto-form over the enolate-form (liquid phase), While the IR suggested both phases.



14



15

Compound **14** assignments over the isomeric structure **15** was inferred over the facts deduced from both IR spectrum and ^{1}H-NMR. In its IR spectrum there are no absorption bands in the region of 2500- 3000 cm^{-1}, which strongly suggest there is no hydrogen bonds which would be the case if the reaction product had the structure **15**. The ^{1}H-NMR spectrum showed absolutely no coupling between the methylene group and the NH group which confirm the existence of compound **14** and not the isomeric form **15**. The rest of spectral and elemental analyses are compatible with structure **14** {E*xperimental}*.

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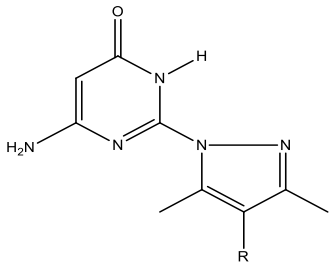
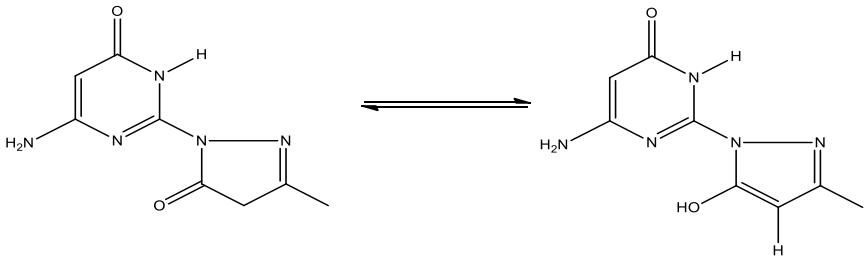
The action of both reagents 2,4-pentanedione or 3-chloro-2,4-pentanedione on compound **3** with deliver the class compound **16.**



16a,R=H
16b,R=Cl

Heating under reflux compound **3** with ethyl acetoacetate furnish the cyclized product **17.**



17a **17b**

Compound **17** existed in the keto-enol form **17a** and **17b** respectively. The keto-form is predominate in solid state phase as the *ir spectrum* show the 2 amidic carbonyl groups at 1680 and 1670, while the hydroxyl group of structure **17b** showed as reduced shape at 3550. In the liquid phase structure **17** prefer the existence in the enol form **17b** as ^{1}HNMR spectrum (DMSO-d_6) show the existence of pyrazole methine as well as the phenolic hydroxyl group at 05.32 ppm and 06.73 and show no detection at all for the methylene group of **17a** {*Experimental}.*

From the above we can deduce that equilibrium of compound **17** prefer the keto-form in solid-state while it goes toward the enol form in liquid-state.

Experimental

Solid compounds were re-crystallized to constant melting points and dried in vacuum in drying pistol containing sodium hydroxide. All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus. Micro analyses were carried out at the Micro analytical unite National Research Centre. IR spectra were carried out on FT/IR 300 E Jasco using KBr discs. 1H-NMR spectra were measured in DMSO, using Joel Ex. 270 NMR spectrometer. Signals were measured with reference to TMS as an internal standard. The Mass spectra were recorded on Finnigan SSQ 7000 spectrometer.

All reactions were followed up by TLC using CHCl/MeOH (9:1, v/v) and/or ethyl acetate/Benzene (7:3) and detected under UV Lamp.

2-arylmethylenehydrazino-3,4-dihydro-6-aminopyrimidin-4-ol 5a-c

General procedure

A mixture of compound 3 (1.41g, 10.00 mmol) and an equimolecular amount of the appropriate aldehyde (10mmol) in 50 ml of absolute ethanol was refluxed for 5h. The reaction mixture was poured onto ice water. The solid that formed was collected by filtration, dried and crystallized from the proper solvent.

2-(4-methoxybenzylidene)hydrazino-3,4-dihydro-6-aminopyrimidin-4-ol (5a)

From compound 3 (1.41 g, 10 mmol) and p-anisaldehyde (1.36g, 10 mmol).The compound 5a was separated as yellow powder, crystallized from DMF(dimethylforrnnmide); m.p310-312oC with 80%yield; IR (KBr) (vmax, cm-1):3500 (OH), 3250(NH2)and 3100(NH). 1HNMR (DMSO-d6): δppm = 3.80(s, 3H,OMe), 4.70(s, 1H, pyrimidine methine proton), 6.20(br.s, 2H, NH2,disappeared after D2O exchange), 6.96(d, 2H, J=9Hz, A-B system of the aromatic ring), 7.88(d, 2H, J=9Hz, A-B system of the aromatic ring) and 7.99(s, 1H, methine proton of Schiff's base) and 11.00(br.s, 1H,OH, disappeared after D2O exchange). Anal. Calcd for C12H13N5O2 (259.26): C(55.59%) H(5.05%) N(27.01%)Found: C(55.49%) H(5.17%) N(26.36%).

2-(4-dimethylaminobenzylidene)hydrazino-3,4-dihydro-6-aminopyrimidin-4-ol (5b)

From compound 3 (1.41 g, 10 mmol) and 4-(dimethylamino)benzaldehyde (1. 49 g, 10 mmol).The compound 5b was separated as deep red powder, crystallized from DMF; m.p. 303-305oC with 95%yield; IR (KBr) (vmax, cm-1):3450 (OH), 3270(NH2)and 3100(NH). 1HNMR (DMSO-d6): δppm = 2.96(s, 6H,NMe2), 4.63(s, 1H, pyrimidine methine proton), 6.12(br.s, 2H, NH2,disappeared after D2O exchange), 6.70(d, 2H, J=9Hz, A-B system of the aromatic ring), 7.67(d, 2H, J=9Hz, A-B system of the aromatic ring) and 7.91(s, 1H, methine proton of Schiff's base) and 10.53(br.s, 1H,OH, disappeared after D2O exchange). Anal. Calcd for C13H16N6O (272.31): C(57.34%) H(5.92%) N(30.86%) Found: C(56.36%) H(6.04%) N(30.28%).

2-benzylidenehydrazino-3,4-dihydro-6-aminopyrimidin-4-ol (5c)

From compound 3 (1.41 g, 10 mmol) and benzaldehyde (1. 06 g, 10 mmol).The compound 5C was separated as yellow powder, crystallized from methanol; m.p249-250oC with 90%yield; IR (KBr) (vmax, cm-1):3500 (OH), 3260(NH2), 3100(NH) and 1680 (CO) 1HNMR (DMSO-d6): δppm 4.75(s, 1H, pyrimidine methine proton), 6.15(br.s, 2H, NH2,disappeared after D2O exchange), 7.42(m, 3H, m&p-phenyl ring protons), 7.90(d, 2H, J=9Hz, o-phenyl ring) and 8.02(s, 1H, methine proton of Schiff's base) and 11.42(br.s, 1H,OH, disappeared after D2O exchange). Anal. Calcd for C11H11N5O (229.24): C(57.63%) H(4.84%) N(30.55%) Found: C(56.32%) H(4.63%) N(29.98%).

2-(4-chlorobenzylidene)hydrazino-3,4-dihydro-6-(4-chlorobenzylidene)-aminopyrimidin-4-ol (6)

A mixture of compound 3 (1.41g, 10.00 mmol) and an dual molecular amount of the 4-chloroaldehyde (2.80 g, 20mmol) in 50 ml of absolute ethanol was refluxed for 5h. The reaction mixture was poured onto ice water. The solid that formed was collected by filtration, dried and crystallized from DMF, m.p. 315-317 oC with 89% yield; IR (KBr) (vmax, cm-1): 3150-3100(NH) and 1682 (CO); 1HNMR (DMSO-d6): δppm 5.54(s, 1H, pyrimidine methine proton), 6.42(br. S., 2H, 2 NH, disappeared after D2O exchange), 7.13(d, 2H, J=8Hz, A-B system of the aromatic ring), 7.26(d, 2H, J=8Hz, A-B system of the aromatic ring), 7.39(d, 2H, J=8Hz, A-B system of the aromatic ring), 7.96(d, 2H, J=8Hz, A-B system of the aromatic ring)and 7.99(s, 2H, the 2methine protons of Schiff's bases). Anal. Calcd for C18H13Cl2N5O (386.23): C(55.97%) H(3.39%) Cl(18.36%) N(18.13%) Found: C(56.01%) H(3.30%) Cl(18.02%) N(17.75%).

5-Bromo-2-(4-methoxybenzylidene)hydrazino-3,4-dihydro-6-aminopyrimid- in-4-ol (7)

To a solution of 2.59 g (10 mmol) of 4b in 30 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate, 1.59 g (10 mmol) of bromine in 15 ml of acetic acid was gradually added with shaking. The whole was heated on a water bath for 3 hours, left to cool and poured into water. The precipitate, that separated, was collected, washed thoroughly with water, dried and crystallised from DMF, m.p. 250 oC with 60% yield. The IR spectrum displays bands at: 3150 (broad NH) and 1675 cm"1 (CO), 1HNMR (DMSO-d6): δppm = 3.87(s, 3H,OMe), 6.50(br.s, 2H, NH2,disappeared after D2O exchange), 6.90(d, 2H, J=9Hz, A-B system of the aromatic ring), 7.80(d, 2H, J=9Hz, A-B system of the aromatic ring) and 8.05(s, 1H, methine proton of Schiff's base) and 11.50(br.s, 1H,OH, disappeared after D2O exchange). Anal. Calcd for C12H12BrN5O2 (338.16): C(42.62%) H(3.58%) Br(23.63%) N(20.71%)Found: C(43.02%) H(3.50%) Br(22.98%) N(21.01%).

6-Bromo-1h,5h-7-amino-3-(4--methoxyphenyl-8-triazolo[4,3-a]pyrimidin-5-one(8)

To a solution of 2.59 g (10 mmol) of 4b in 30 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate, 3.18 g (20 mmol) of bromine in 15 ml of acetic acid was gradually added with stirring. The whole solution was heated on a water bath for 3 hours, cooled and poured into ice-water. The solid, so formed, was filtered off, washed with water, dried and crystallized from DMF, m.p. 310 oC with 55% yield. The IR spectrum displays bands at: 2999 (broad, NH with hydrogen bond) and 1699 cm-1 (CO)., 1HNMR (DMSO-d6): δppm = 3.92(s, 3H,OMe), 6.80(br.s, 2H, NH2,disappeared after D2O exchange), 7.20(d, 2H, J=9Hz, A-B system of the aromatic ring), 8.05(d, 2H, J=9Hz, A-B system of the aromatic ring) and the NH proton spreads over all the spectrum). Anal. Calcd for C12H10BrN5O2 (336.14): C(42.88%) H(3.00%) Br(23.77%) N(20.83%) Found: C(43.50%) H(2.96%) Br(23.27%) N(20.33%).

7-amino-3-thioxo-2,3-dihydro[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one(12)

A mixture of 1 g of 3, 0.5 g of potassium hydroxide and 3 ml of carbon disulphide was heated under reflux in 50 ml of ethanol for 14 hours. After of ethanol was evaporated, water was added and the alkaline solution was filtered. The clear filtrate was acidified with dilute hydrochloric acid and the formed precipitate was collected and crystallized from DMF, m.p. >380 oC with 50% yield. The IR spectrum displays bands at: 3300 (NH2) 3200 (broad NH) and 1710 cm-1 (CO), 1HNMR (DMSO-d6): δppm = 4.49(s, 1H, pyrimidine methine proton), 6.90(br.s, 2H, 2 NH groups,disappeared after D2O exchange).and 7.20(br.s, 2H, NH2,disappeared after D2O exchange) Anal. Calcd for C5H5N5OS (183.19): C(32.78%) H(2.75%) N(38.23%) S(17.50%) Found: C(32.08%) H(2.82%) N(39.03%) S(16.99%)

8-amino-2H-pyrimido[2,1-c][1,2,4]triazine-3,6(1H,4H)-dione(14)

A solution of 3 (1.41 g, 10 mmol) in 40 ml of anhydrous dioxane was gradually treated with 1.13 g (10 mmol) of chloroacetyl chloride with stirring. The reaction solution was left stirring overnight. The next day, the reaction mixture was poured on solution of 0.5 g of sodium acetate in 10 ml of water and warmed for 5 minutes. The solid, thus separated, was collected, washed with water, dried and crystallized from ethanol, m.p. >250-251 oC with 55% yield. The IR spectrum displays bands at: 3450 (OH), 3300 (NH2) 3100 (broad NH) and 1710&1695 cm-1 (2CO), 1HNMR (DMSO-d6): δppm = 4.29(s, 1H, pyrimidine methine proton), 4.82(s, 2H, methylene group), 6.80(br.s, 2H, NH2,disappeared after D2O exchange) and 7.45 br.s, 2H, 2 NH groups,disappeared after D2O exchange). Anal. Calcd for C6H7N5O2 (181.15): C(39.78%) H(3.89%) N(38.66%) Found: C(40.10%) H(3.75%) N(37.99%).

3,4-Dihydro-2-(4`,5`-disubstituted-3-methylpyrazol-1`-yl)-6-amino-4-oxopyrimidine 16$_{a,b}$General procedure

To a solution of 3 (1.41 g, 10 mmol) in 50 rnl of absolute ethanol 10 mmol of each of 2,4-pentancdione (1.00 g), 3-chloro-2,4-pentanedione (1.35 g) was added. The reaction mixture was refluxed for 5 hours, concentrated and cooled. The crystalline solid separated was filtered off and crystallized from the proper solvent to yield compound 16a,b

6-amino-2-(3,5-dimethyl-1H-pyrazol-1-yl)pyrimidin-4(3H)-one 16$_a$

From compound 3 (1.41 g, 10 mmol) and 2,4-pentancdione (1. 00 g, 10 mmol).The compound 16a was separated as colorless powder, crystallized from ethanol; m.p. 249-250oC with 70 % yield; IR (KBr) (vmax, cm-1): 3450 (OH), 3300 (NH2) and 3200(NH) . 1HNMR (DMSO-d6): δppm = 2.16(s, 3H,Me), 2.55(s, 3H, Me), 5.15(S, 1H, CH pyrimidine), 6.11(s, 1H, CH pyrazole), 6.68(br s, 2H, disappeared after D2O exchange, NH2) and and 10.92(br.s, 1H, OH, disappeared after D2O exchange). Anal. Calcd for C9H11N5O (205.22): C(52.67%) H(5.40%) N(34.13%)Found: C(52.79%) H(5.41%) N(34.20%)

6-amino-2-(4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)pyrimidin-4(3H)-one 16$_b$

From compound 3 (1.41 g, 10 mmol) and 3-chloropentane-2,4-dione (1. 35 g, 10 mmol).The compound 16bwas separated as yellow powder, crystallized from ethanol; m.p. 199-200oC with 70 % yield; IR (KBr) (vmax, cm-1): 3500 (OH), 3250 (NH2) and 3150(NH) . 1HNMR (DMSO-d6): δppm = 2.21(s, 3H,Me), 2.38(s, 3H, Me), 5.50(s, 1H, CH pyrimidine), 7.38(br s, 2H, disappeared after D2O exchange, NH2) and and 11.32(br.s,

1H, OH, disappeared after D2O exchange). Anal. Calcd for C9H11N5O (239.66): C(45.10%) H(4.21%) Cl(14.79%) N(29.22%) Found: C(45.09%) H(4.20%) Cl(14.80%) N(29.27%) .

6-amino-2-(5-hydroxy-1H-pyrazol-1-yl)pyrimidin-4(3H)-one 17

To a solution of 3 (1.41 g, 10 mmol) in 50 rnl of absolute ethanol ethyl 3-oxobutanoate (1. 30 g, 10 mmol). was added. The reaction mixture was refluxed for 25 hours, followed by TLC control. The reaction mixture was evaporated in vacuo to furnish the title compound as colourless powder, crystallized from methanol; m.p. 180-181oC with 75 % yield. IR (KBr) (vmax, cm-1): 3550 (OH) [17b], 3300 (NH2) , 3125(broad NH) and 1680 &1670 cm-1 (2CO), 1HNMR (DMSO-d6): δppm = 2.17(s, 3H,Me), 5.15(s, 1H, CH pyrimidine), 5.34(s, 1H, CH pyrazole), 6.85 (br s, 2H, disappeared after D2O exchange, NH2) and and 7.70(s, 1H, NH, disappeared after D2O exchange). Anal. Calcd for C8H9N5O2 (320.13): = C(46.38%) H(4.38%) N(33.80%) O(15.44%) Found: C(46.48%) H(4.37%) N(33.70%)

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