Antioxidant Activity of Novel Pyrimidines Derived from Arylidenes

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ABSTRACT
Arylidenes have been utilized as a scaffold for synthesis of different heterocyclic compounds such as thiazolo[3,2-a]pyridine, pyridinium salt of pyrano[2,3-d]pyrimidine and 2-thioxotetrahydropyrimidine derivatives. The effect of acidic medium, different nucleophiles and/ or electrophiles has been studied on thioxotetrahydropyrimidine derivative. The synthesized compounds have been screened for their in vitro antioxidant activity.

Key words: Arylidene, Tetrahydropyrimidine, Thiazolo[3,2-a]pyridine**,** Pyridinium salt of pyrano[2,3-d]pyrimidinecarboxylic acid, Antioxidant activity.

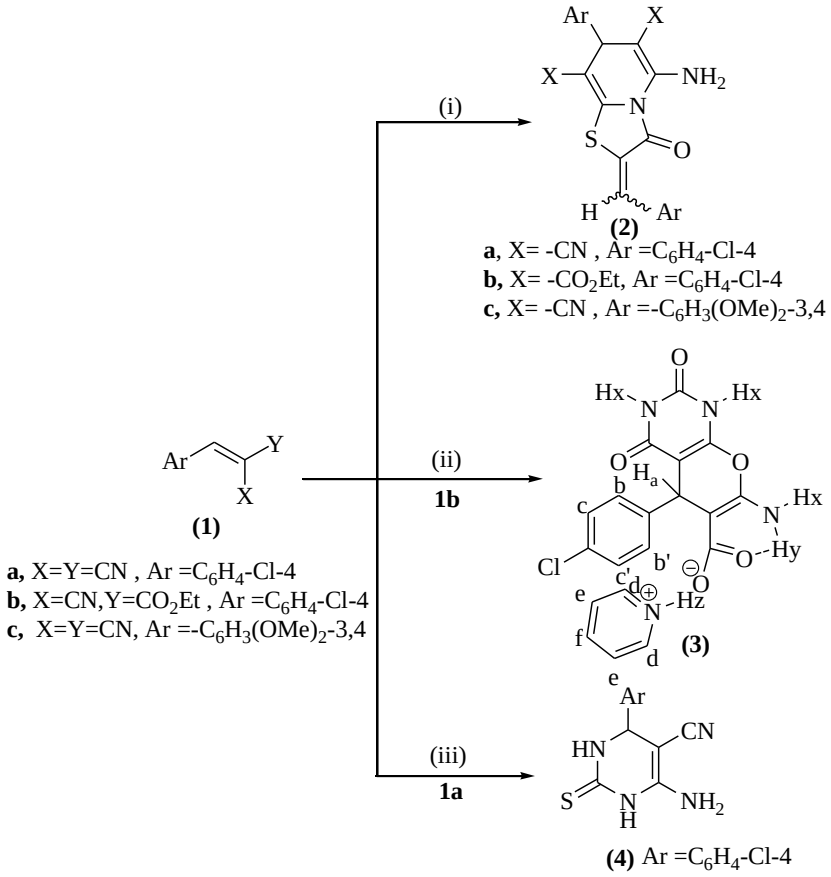
INTRODUCTION

The utility of activated nitriles in synthesis of a wide variety of heterocyclic systems encourages us to synthesize pyrimidine moiety as an important class of nitrogen containing heterocycles [1] which is widely used as a key building block for pharmaceutical agents. Pyrimidine derivatives exhibit antibacterial [2,3], antifungal [4], antiviral [5], analgesic [6-8], antihypertensive activities. They are considered calcium channel blocker [9-11], antioxidant [12], anti-inflammatory [13-15], anticancer drugs [16]. Pyrimidines are not only unique HIV reverse transcriptase inhibitors [17,18] but also they have anti-tumor activity [19].
In continuation of our previous works [20-25], the present work aimed at utilization of the reactivity of arylidenes towards different nucleophiles to design, construct new heterocyclic compounds and study their biological activities as antioxidant agent.

RESULT AND DISCUSSION

The arylidene of active methylene compounds **1a-c** were prepared according to the described procedure [26] and they were allowed to react with different nucleophiles such as thioglycolic acid, barbituric acid and thiourea. Refluxing a mixture of arylidene **1a-c** and thioglycolic acid in ethanol containing triethylamine, gave 7H-thiazolo[3,2-a] pyridine derivatives **2a-c**. In literature [27] the way of their formation was given but the configuration assignment at C-2 was not discussed. In the present investigation, we present a new finding consisting in the existence of this type of compounds as a mixture of two geometrical isomers *E*- and *Z*- as evidenced from their ^{1}H-NMR spectra. ^{1}H-NMR spectrum (500 MHz) of compound **2b** revealed the existence of the structure in two geometrical isomers *E*- and *Z*-.Both the methine and olefinic protons appear as two spaced singlets in a ratio of ≈ 2:1, respectively, based on the integration of olefinic protons singlets. It is worth to mention that the olefinic proton of *Z*-isomer (7.68 ppm) is relatively deshielded by the 4-oxo group of the thiazolo moiety as compared with the *E*-counterpart (7.56 ppm). This relationship is acceptable in the elucidation of the configuration of arylidene derivatives of azalactones [28], indolones [29, 30] and pyrazolin-5-ones [31]. The 7H-thiazolo[3,2-a]pyridine derivatives **2a,c** exhibit the same manner in their ^{1}H-NMR spectra.
When the reaction of barbituric acid with activated nitrile **1b** was conducted in refluxing pyridine, the pyridinium salt **3** was obtained in a good yield. The formation of compound **3** is

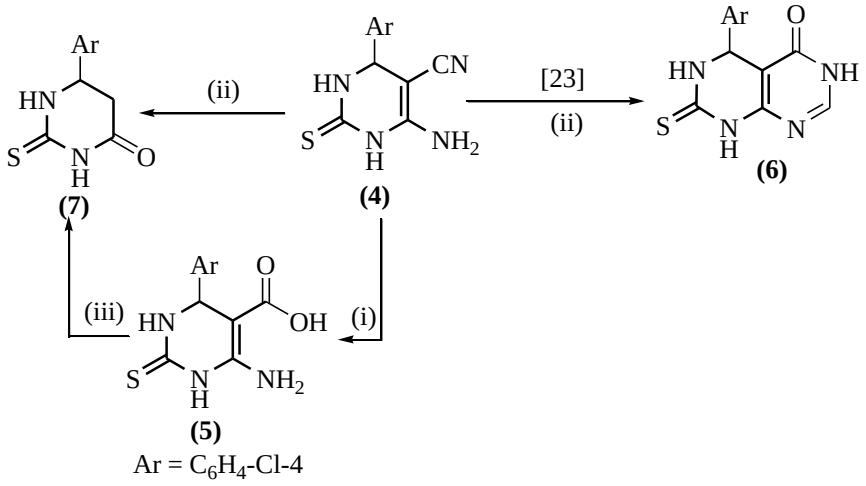
assumed to proceed *via* the initial Michael addition to yield acyclic Michael adduct which then cyclized followed by hydrolysis to give the pyridinium salt **3**. On the other hand, the attack of thiourea at the β-carbon of **1a**, followed by another attack at cyano group and cyclization, or vice versa, gives 6-amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(4)**. It has been reported [32,33] that when the reaction was conducted as one pot three-component reaction *via* reaction of p-chlorobenzaldehyde, malononitrile and thiourea under the same reaction conditions or by using phosphorous pentoxide instead of sodium ethoxide, the product obtained was identified as 2-mercaptopyrimidine not as the separated product in our laboratory *viz* 1,2,3,4-tetrahydropyrimidine. The structure of the tetrahydropyrimidine derivative **4** has been determined from their analytical and spectral data namely; IR, ^{1}H-NMR and MS spectra which are in a good agreement with the assigned structure **4** (cf. Scheme 1).



(i) Thioglycolic acid, EtOH, Et_3N, reflux; (ii) Barbituric acid, pyridine, reflux; (iii) Thiourea, EtONa, reflux

Scheme 1

The high functionality of tetrahydropyrimidine derivative **4** prompted us to study the effect of acidic medium, nitrogen nucleophiles and different electrophiles on tetrahydropyrimidine derivative **4**. The effect of strong acid such as sulfuric acid on tetrahydropyrimidine derivative **4** at room temperature afforded 6-amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid **(5)** *via* hydrolysis of cyano group into carboxylic acid (cf. Scheme 2).

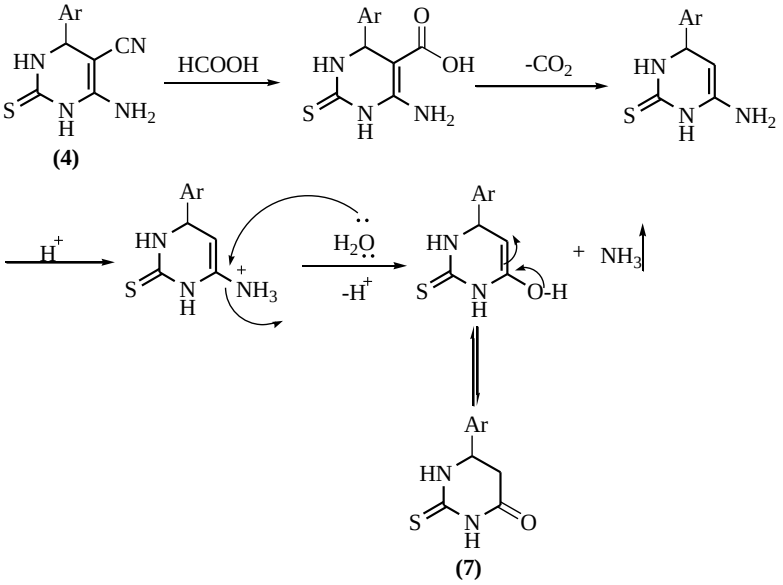


Ar = C_6H_4-Cl-4

(i) H_2SO_4, rt; (ii) HCOOH, reflux; (iii) AcOH, reflux;

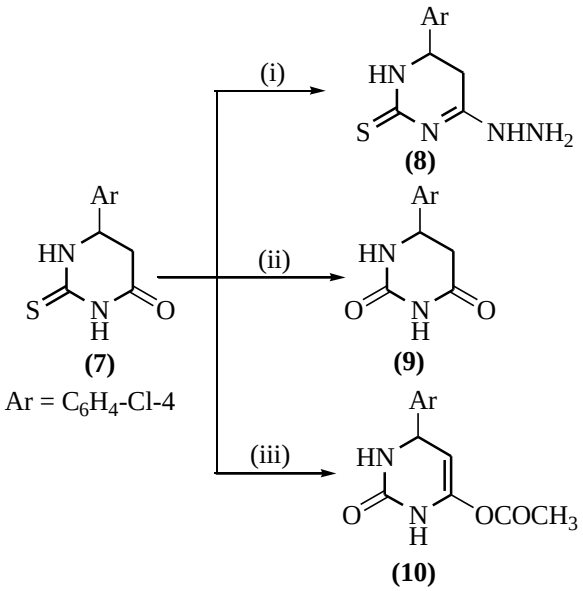
Scheme 2

In one of our previous publications [23], it has been reported that, the effect of boiling formic acid on tetrahydropyrimidine derivative **4** resulted in pyrimidin-4-(3*H*)-one derivative **(6)**. Contrary to the above publication, reaction of formic acid with tetrahydropyrimidine derivative **4** under reflux gave 6-(4-chlorophenyl)-2-thioxo-hexahydropyrimidine-4(1H)-one **(7)**.The ^{1}H-NMR spectrum of (7) in DMSO disclosed an ABX pattern consistent with Ar-CH_X-CH_AH_B-CO- moiety in which each of these coupled protons appears as a doublet of doublets with a germinal J= 16.8Hz and vicinal coupling constant of 5.4 & 6.3 Hz. The formation of **7** can be explained according to our speculation, by a plausible mechanism which involves complete hydrolysis of cyano group into carboxylic group then decarboxylation and deamination (cf. Scheme 3). The plausible mechanism has been confirmed *via* the isolation of the same hexahydropyrimidine-4(1H)-one **7** by the reaction of compound **5** with acetic acid under reflux.



Scheme 3

The structural features of 6-(4-chlorophenyl)-2-thioxo-hexahydropyrimidine-4(1H)-one **(7)** has been chemically proven *via* reaction with hydrazine hydrate, alcoholic sodium hydroxide and / or acetic anhydride to give hydrazinyldihydro-pyrimidinthione **(8)**, hexahydropyrimidindione **(9)**, 2-oxo-tetrahydropyrimidinyl acetate derivatives **(10)**, respectively **(**cf. Scheme 4).

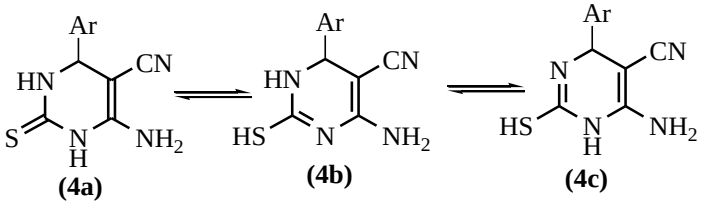


(i) $N_2H_4.H_2O$, EtOH, reflux; (ii)alc NaOH, 10%, reflux; (iii) Ac_2O, reflux

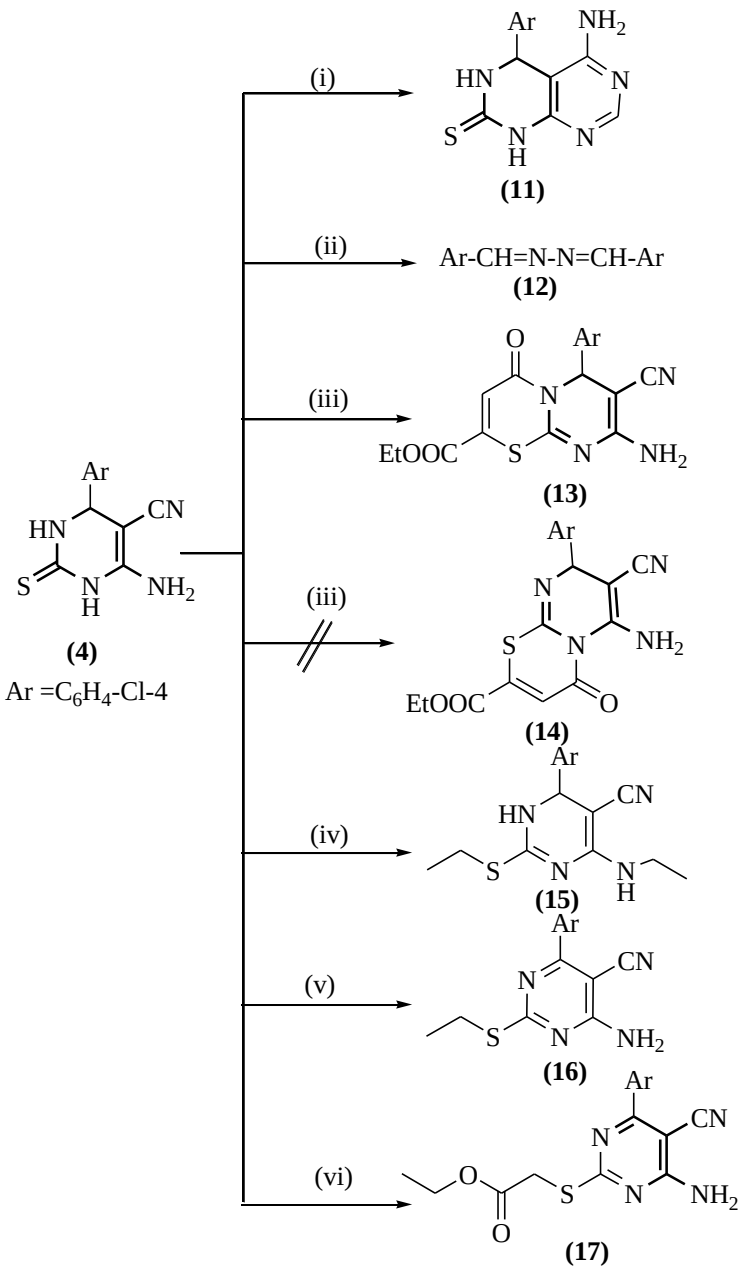
Scheme 4

Treatment of the tetrahydropyrimidine **4** with formamide and / or hydrazine hydrate gave aminopyrimidopyrimidine derivative **11** and 4-chlorobenzaldehyde azine **(12),** as a result of reaction of the aldehyde resulted from cleavage of tetrahydropyrimidine **4** respectively. The structure of **12** was chemically confirmed by comparison with an authentic sample (mp, mixed mp and TLC) prepared from 4-chlorobenzaldehyde with hydrazine hydrate in refluxing ethanol.

The tetrahydropyrimidine **4** exists in a dynamic equilibrium mixture of three tautomeric forms (**4a-c**), the tautomer **4b** is the most thermodynamically stable one due to the presence of two conjugated double bonds. The reaction occurs by the attack of the more nucleophilic sulfur atom rather than the less nucleophilic nitrogen on the electrophilic centers of the reagents. So reaction of tetrahydropyrimidine **4** with diethyl but-2-ynedioate resulted in annulations through formation of 4,6-dihydropyrimido[2,1-b][1,3]thiazine-2-carboxylate derivative **13** rather than 4,8-dihydropyrimido[2,1-b][1,3] thiazine **14** .



Alkylation of tetrahydropyrimidine **4** under different conditions has been investigated. The alkylated product depends upon the strength of the basic catalyst used. In a strong basic ethanolic sodium ethoxide solution, the isolated product revealed S- and N-ethylated one to afford **15,** whereas in ethanol containing sodium acetate as a weak basic catalyst, only S-ethylated product **16** was obtained. Treatment of tetrahydropyrimidine **4** with ethyl chloroacetate in the presence of fused anhydrous sodium acetate furnished ethyl 2-(4-amino-6-(4-chlorophenyl)-5-cyanopyrimidin-2-ylthio)acetate **(17)**. Isolation of S-alkylated product **17** prompted us to claim that in the presence of sodium acetate as a basic catalyst, S-alkylation is occurred rather than N-alkylation in 6-amino-pyrimidin-2-thiones (**17**) **(**cf. Scheme 5).

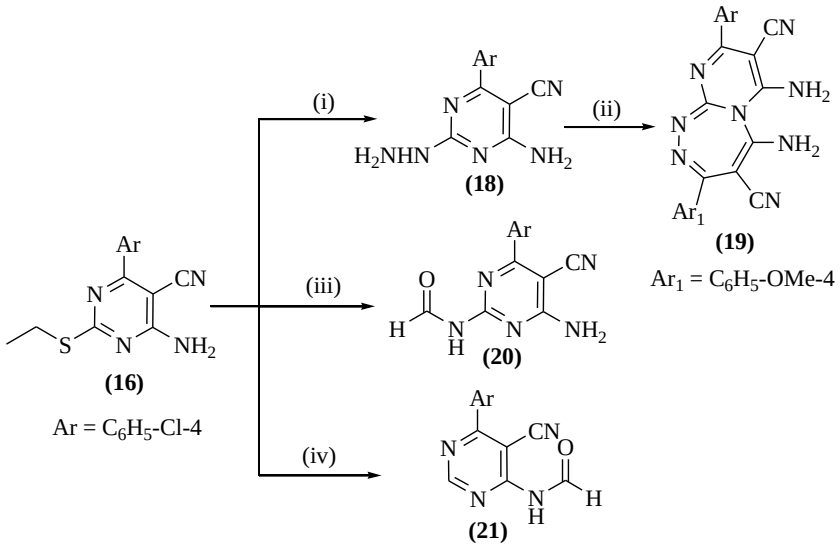


(i) $HCONH_2$,reflux; (ii) $N_2H_4.H_2O$, EtOH, reflux; (iii) EtOOC−C≡C−COOEt , EtOH, reflux;

(iv) EtI / EtONa, stirring; (v) EtI/ EtOH, AcONa; (vi) Ethyl chloroacetate, EtOH, AcONa

Scheme 5

Hydrazinolysis of enaminonitrile **16** with hydrazine hydrate in boiling ethanol afforded 2-hydrazinylpyrimidine derivative **18** which underwent cyclization by reaction with arylidene in dimethylformamide (DMF) to afford compound **19**. Treatment of enaminonitrile **16** with formamide and / or formic acid resulted in N-formamide derivatives **20** and **21,** respectively.



(i) $N_2H_4.H_2O$, EtOH, reflux; (ii) 2-(4-Methoxybenzylidene)malononitrile, DMF, reflux;

(iii) $HCONH_2$, reflux; (iv) HCOOH, reflux

Scheme 6

PHARMACOLOGY

ANTIOXIDANT EVALUATION

The antioxidant activities of the synthesized compounds were shown in table 1. The results revealed that all compounds were found to be potent. Moreover, the results showed that nearly three compounds **8**, **11** and **16** were found to be the most potent levels of activity. Additionally, compounds **2a**, **2b**, **4**, **12, 18** and **19** were found to be moderate activity.

TABLE 1: Total antioxidant capacity of the synthesized compounds.

Compound No.	Total antioxidant capacity (mg AAE*/g compound)
2a	189.25 ± 4.80
2b	106.25 ± 4.61
2c	70.70 ± 2.50
3	61.40 ± 4.0
4	252.45 ± 4.16
5	50.69 ± 1.70
7	68.30 ± 2.0
8	562.0 ± 5.03
9	14.0 ± 2.30
10	76.0 ± 8.71
11	449.96 ± 1.20
12	241.33 ± 2.66
13	65.30 ± 5.20
15	83.49 ± 2.35
16	506.66 ± 4.05
17	66.65 ± 2.0
18	186.50 ± 5.29
19	134.59 ± 8.66
20	51.29 ± 1.76
21	31.35 ± 2.90

Results are (means ± S.D.) (n = 3)
***AAE (Ascorbic Acid Equivalent)**

EXPERIMENTAL

All melting points were measured on Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded using KBr disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H-NMR spectra were run at 300 MHz and /or 500 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as internal standard in deuterated chloroform or deuterated dimethylsulphoxide. Chemical shifts are quoted δ. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. All the spectral measurements as well as elemental analyses were carried out at Micro analytical Center of Cairo University and Main Defense Chemical Laboratory, Egypt. All the newly synthesized compounds gave satisfactory elemental analyses.

Reaction of arylidene 1a-c with thioglyclic acid:

A mixture of arylidene **1a-c** (10 mmol), thioglyclic acid (0.7 ml, 10 mmol) and triethylamine (1 ml) was refluxed in boiling ethanol (30 ml) for 2-3h. The solid product that deposited on hot was collected by filtration, dried and recrystallised from the suitable solvent to give **2a-c**.

2-(4-Chlorobenzylidene)-5-amino-7-(4-chlorophenyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (2a).Pale brown crystals, mp 270-272 °C, lit. mp 254-255°C [27] DMF (dimethylformamide), yield 72 %, FT-IR (KBr, cm^{-1}): 3390, 3289 (NH_2), 3021 (CH aromatic), 2926, 2884 (CH aliphatic), 2209, 2185 (CN), 1707 (C=O), 1657 (C=N), 1561 (C=C), 822 ($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300MHz): 7.95 (s, 1H, Z-isomer, minor, =CH), 7.87 (s, 1H, E-isomer, major, =CH), 7.63 (s, 2H, D_2O-exchangeable, NH_2), 7.66, 7.46 (2 dd, 8H, *J*=7.8 and 4.1Hz, Ar-H), 4.68 (s, 1H, benzylic proton). MS (m/z(%)): 450 ($M^{\ddagger}$, missed), 287 ($M^{\ddagger}$ -4-ClC_6H_4-CH=C=O, 27), 286 (27), 170 (36), 168 (100), 167 (23), 133 (36), 132 (27), 125 (41), 121(32), 99 (32), 98 (46), 97 (64), 93(32), 89 (50), 88 (27), 86 (46), 85 (64), 84 (36), 83 (18), 82 (14), 79 (36), 71(14).

Diethyl 2-(4-chlorobenzylidene)-5-amino-7-(4-chlorophenyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6,8-dicarboxylate (2b). Yellow crystals, mp 240-242°C, lit. mp 235-236°C [34], (ethanol), yield 84%. FT-IR (KBr, cm^{-1}): 3390, 3270 (NH_2), 2960, 2930, 2904 (CH aliphatic), 1706 (br., C=O ester), 1663 (C=O), 1621(C=N and /or C=C), 823($\delta_{2\text{-H}}$). ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.63 (br.s, 2H, D_2O-exchangeable, NH_2), 7.68 (s, 1H, Z-isomer, minor,=CH), 7.56 (s, 1H, E-isomer, major,=CH), 7.17-7.54 (m, 8H, Ar-H), 4.88 (s, 1H, benzylic proton)**,** 1.18 and 1.24 (2 t, 6H, 2-$COOCH_2\underline{CH_3}$, *J* =6.9 Hz), 4.12 (q, 4H, $2COO\underline{CH_2}CH_3$, *J* =6.9 Hz), MS(m/z(%)): 544 ($M^{\ddagger}$, missed), 473 ($M^{\ddagger}$ -$CO_2CH=CH_2$ & H, 3), 471 ($M^{\ddagger}$ -$HCO_2C_2H_5$, 5), 435 (39), 434 (29), 433 (100), 432 (89), 405 (7), 387 (9), 315(9), 168 (21), 167 (9) 136 (9).

2-(3,4-Dimethoxybenzylidene)-5-amino-7-(3,4-dimethoxyphenyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a] pyridine-6,8-dicarbonitrile (2c). Pale brown crystals, mp 266-268°C, DMF (dimethylformamide), yield 72 %. FT-IR (KBr, cm^{-1}): 3376, 3278 (NH_2), 3067(CH aromatic), 2994, 2963, 2938, 2907, 2838 (CH aliphatic), 2196 (CN), 1710 (C=O), 1653 (C=N), 1593, 1557 (C=C), 803 ($\delta_{2\text{-H}}$). ^{1}HNMR (DMSO-d_6, 300MHz): 7.86 (s, 1H, Z-isomer, minor, =CH), 7.80 (s, 1H, E-isomer, major, =CH), 7.49 (s, 2H, D_2O-exchangeable, NH_2), 6.89-7.28 (m, 6H, Ar-H), 4.53 (s, 1H, benzylic proton), 3.77, 3.78, 3.83, 3.85 (4s, 6H, 4(-OCH_3)). MS (m/z(%)): 502 ($M^{\ddagger}$, 16), 365 ($M^{\ddagger}$ - $C_6H_3(OMe)_2$-3,4-, 46), 364 (13), 194 (50), 179 (13), 147 (11), 73 (52), 72 (18), 67 (13), 66 (100), 65 (22).

Reaction of arylidene (1b) with barbituric acid; formation of pyridinium-7-amino-2,4-dioxo-5(4-chlorophenyl)-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (3):

A mixture of arylidene **1b** (1.18 g, 5 mmol), barbituric acid (0.65 g, 5 mmol) was refluxed in pyridine (15 ml) for 0.5 h. Left to cool, the crude solid product that deposited after cooling was collected by filtration, dried and recrystallised from ethanol the pyridinium salt **3** as white crystals, mp > 300°C, yield 67 %. FT-IR (KBr, cm^{-1}): 3411, 3200 (NH_2&NH), 3138 (CH aromatic), 2948, 2848 (CH aliphatic), 1700 (C=O), 1609 (C=N and/ or C=C), 844 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300MHz): 11.39 & 11.25 (each s, 2H, D_2O-exchangeable, $2NH_y$), 11.10 (s, 1H, D_2O-exchangeable, NH_z), 10.12 (s, 3H, D_2O-exchangeable, $3NH_x$), 8.78 (m, 2H, Ar-H_d), 8.26 (d, 1H, Ar-H_c, J = 8.7 Hz), 8.07 (d, 1H, Ar-$H_{c'}$, J = 8.7 Hz), 7.80 (m, 2H, Ar-H_e), 7.53 (d, 1H, Ar-H_f, J = 8.7 Hz), 7.19 (d, 1H, Ar-H_b, J = 8.1 Hz), 7.03 (d, 1H, Ar-$H_{b'}$, J = 8.4 Hz), 5.88 (s, 1H, H_a).

6-Amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4)

A mixture of arylidene **1a** (1.88 g, 10 mmol) and thiourea (0.76 g, 10 mmol) in sodium ethoxide solution (0.23 g of sodium metal in 25 ml dry ethanol) was heated under reflux for 4h, the reaction mixture was cooled, then acidified with cold hydrochloric acid (2 N, 3 ml), the solid product that formed was filtrated off, dried and recrystallization from toluene/ethanol (4:1) to afford enaminonitrile **4** as yellow crystals, mp 221-223°C, yield 84 **%**. FT-IR (KBr, cm-1): 3403, 3327, 3201 (NH_2 & NH), 3020 (CH aromatic), 2185 (C≡N), 1663 (C=N), 1189 (C=S), 833 ($\delta_{2\text{-}H}$). ^{1}H-NMR (300 MHz, DMSO-d_6): 10.05, 9.78 (2s, 2H, D_2O-exchangeable, 2NH), 7.47(dd, 2H, J_o = 6.3, J_m =2.1, Ar-H), 7.26-7.23 (dd, 2H, J_o = 6.9, J_m =2.1, Ar-H), 6.20 (s, 2H, D_2O-exchangeable, NH_2) and 5.03 (s, 1H, benzylic proton). MS (m/z(%)): 264 $(M]^{\dot{+}}$, 44), 262 (22), 153 (100), 111 (41) and 91 (77).

6-Amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (5)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol) in concentrated sulphuric acid (20 ml) below 5 °C and kept for 48 h at room temperature. The content was poured into ice cold water and filtered. The product was isolated and recrystallized from benzene/ methanol (4:1) to afford **5** as yellow crystals, mp 300-302 °C, yield 70%. FT-IR (KBr, cm^{-1}): 3455, 3353, 3319 (OH& NH_2& NH), 3182 (CH aromatic), 1705 (C=O acid), 828 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300MHz): 11.34 (s, 1H, D_2O-exchangeable, OH), 10.02 (s, 1H, D_2O-exchangeable, NH), 7.66 (s, 1H, D_2O-exchangeable, NH), 7.49-6.90 (m, 4H, Ar-H), 5.15 (s, 1H, benzylic proton) and 3.51 (s, 2H, 1H, D_2O-exchangeable, NH_2). MS (m/z(%)): 285 $(M+2]^{\dot{+}}$, 2), 284 $(M+1]^{\dot{+}}$, 2), 283 $(M]^{\dot{+}}$, 2), 265 (17), 165 (10), 140 (36), 127 (34), 125 (100) and 64 (22).

6-(4-Chlorophenyl)-2-thioxo-hexahydropyrimidine-4(1H)-one (7)

Method A:

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), in formic acid (20 ml) was refluxed for 27 h. Left to cool, then collect the crude solid product that precipitated out by filtration by suction and recrystallized from acetic acid to afford **7** as white crystals, mp 270-271 ^oC, yield 86%. FT-IR (KBr, cm^{-1}): 3176 (NH), 3106 (CH aromatic), 2970 (CH aliphatic), 1694 (C=O), 1180 (C=S), 828 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 11.13 (s, 1H, D_2O-exchangeable, NH), 10.00 (s, 1H, D_2O-exchangeable, NH), 7.48 (d, 2H, J = 8.4Hz, Ar-H), 7.29 (d, 2H, J = 8.4Hz, Ar-H), 4.84 (m, 1H, benzylic proton), 2.97 (dd, 1H, J = 16.8 and 6.3Hz, pyrimidinone moiety) and 2.74 (dd, 1H, J = 16.5 and 5.4Hz, pyrimidinone moiety). MS (m/z(%)): 242 $(M+2]^{\dot{+}}$, 39), 241 $(M+1]^{\dot{+}}$, 20), 240 $(M]^{\dot{+}}$, 93), 165 (100), 138 (76), 111 (19) and 102 (32).

Method B:

A solution of **5** (1.41 g, 10 mmol) in glacial acetic acid (25 ml) was heated under reflux for 18 h. The reaction mixture was poured into ice cold water then collected by filtration and washed with water to afford **7**.

4-(4-Chlorophenyl)-6-hydrazinyl-4,5-dihydropyrimidine-2(1H)-thione (8)

A mixture of 2-thioxohexahydropyrimidinone derivative **7** (1.2 g, 10 mmol) and hydrazine hydrate (98%) (0.6 ml, 12 mmol) in boiling ethanol (30 ml) was refluxed for 14 h. The crude solid product that precipitated out was filtered off and recrystallized from ethanol to afford **8** as white crystals, mp 200-201°C, yield 84%. FT-IR (KBr, cm^{-1}): 3405, 3318, 3207 (NH_2&NH), 3013 (CH aromatic), 2872 (CH aliphatic), 1671 (C=N), 821 ($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.95, 8.15 (2 s, 2H, D_2O-exchangeable, 2NH), 7.47-7.28 (m, 4H, Ar-H), 7.13 (s, 2H, D_2O-exchangeable, NH_2), 5.62 (m, 1H, benzylic proton), 2.70 (dd, 1H, J = 16.2 and 5.4 Hz, pyrimidinone moiety) and 2.56 (dd, 1H, J = 14.1 and 6.3 Hz, pyrimidinone moiety). MS (m/z(%)): 256 $(M+2]^{\dot{+}}$, 77), 255 $(M+1]^{\dot{+}}$, 80), 248 (99), 234 (92), 227 (89), 206 (100), 198 (80) and 181 (100).

6-(4-Chlorophenyl)-hexahydropyrimidine-2,4-dione (9)

To a solution of 2-thioxohexahydropyrimidinone derivative **7** (1.2 g, 10 mmol), in alcoholic sodium hydroxide 10 % was refluxed for 12 h. Left to cool, the solid product that formed was filtrated off, dried and recrystallized from ethanol to afford **9** as white crystals, mp 252-255 °C, yield 67%. FT-IR (KBr, cm^{-1}): 3240 (NH), 3080 (CH aromatic), 2897 (CH aliphatic), 1701 (C=O), 823 ($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 10.18, 8.00 (2 s, 2H, D_2O-exchangeable, 2NH), 7.46-7.33 (dd, 4H, Ar-H), 4.69 (m, 1H, benzylic proton), 2.80 (dd, 1H, J = 15.9 and 5.7 Hz) and 2.62 (dd, 1H, J = 16.5 and 7.2 Hz). MS (m/z(%)): 224 $(M]^{\dot{+}}$, 53), 197 (55), 184 (49), 160 (60), 149 (67), 138 (52), 125 (64), 91 (53), 81 (84) and 69 (100).

6-(4-Chlorophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl acetate (10)

A solution of 2-thioxohexahydropyrimidinone derivative **7** (1.2 g, 10 mmol) in acetic anhydride (15 ml) was refluxed for 14 h. Left to cool, then poured onto ice/water, the solid product was collected by filtration dried and then recrystallised from petroleum ether (bp 80-100°C) to afford **10** as yellow crystals, mp 183-184°C, yield 74%. FT-IR (KBr, cm^{-1}): 3236, 3197 (NH), 3140 (CH aromatic), 2999 (CH aliphatic), 1722 (C=Oester), 1680 (C=Oimide), 821($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 12.46, 10.90 (2 s, 2H, D_2O-exchangeable, 2NH), 7.74-7.46 (m, 4H, Ar-H), 7.03 (d, 1H, hexahydropyrimidin moiety, J= 15.6Hz), 6.52 (d, 1H, benzylic proton, J= 16.2 Hz) and 2.26 (s, 3H, -$COCH_3$). MS (m/z(%)): 267 $(M+1]^{\dot{+}}$, 78), 266 ($M^{\dot{+}}$, 86), 250 (84), 230 (72), 212 (80), 148 (90), 111 (64) and 57(100).

5-Amino-4-(4-chlorophenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine-2(1H)-thione (11)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), in formamide (10 ml) was refluxed for 15 h. After cooling, the reaction mixture was poured into ice/water. The precipitated solid was filtered off, washed with water and recrystallized from benzene to afford **11** as pale yellow crystals, mp 178 °C, yield 85 %. FT-IR (KBr, cm^{-1}): 3450, 3332, 3183 (NH_2 & NH), 3042 (CH aromatic), 1631 (C=N), 1092 (C=S), 830 ($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 9.61 & 9.20 (2 s, 2H, D_2O-exchangeable, 2NH), 8.60-7.33 (m, 5H, Ar-H), 6.21 (s, 2H, D_2O-exchangeable, NH_2) and 5.30 (s, 1H, benzylic proton). MS (m/z(%)): 293 $(M+2]^{\dot{+}}$, 19), 292 $(M+1]^{\dot{+}}$, 10), 291($M^{\dot{+}}$, 7), 271 (61), 246 (17), 215 (99), 188 (35), 163 (38), 92 (24) and 64 (100).

4-Chlorobenzaldehyde azine (12)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), hydrazine hydrate (98%) (0.67 ml, 12 mmol) was stirred at room temperature for 8 h. The precipitating solid was filtered off, washed with water and recrystallized from benzene to afford **12** as white crystals, mp 211-214 °C, lit. mp 210 °C [35], yield 72%. FT-IR (KBr, cm^{-1}): 3046 (CH aromatic), 2994 (CH aliphatic), 1621(C=N), 820 ($\delta_{2\text{-H}}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.72 (s, 2H, 2 CH=N-), 7.88 (d, 4H, J_o= 8.4Hz, Ar-H) and 7.60 (d, 4H, J_o= 8.4Hz, Ar-H). MS (m/z(%)): 278 (M+2]

$^{\bullet+}$, 41), 277 (M+1] $^{\bullet+}$, 44), 276 (M] $^{\bullet+}$, 44), 259 (22), 250 (26), 165 (100), 149 (56), 138 (44), 111(67) and 89 (82).

Ethyl 8-amino-6-(4-chlorophenyl)-7-cyano-4-oxo-4,6-dihydropyrimido[2,1-b][1, 3]thiazine-2-carboxylate (13)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), diethyl but-2-ynedioate (0.85 ml, 10 mmol) in ethanol (30 ml) was refluxed for 17 h. The crude solid product that precipitated out was filtered off and recrystallized from ethanol to afford **13** as red crystals, mp 263-265 °C, yield 87%. FT-IR (KBr, cm^{-1}): 3418, 3329 (NH_2), 3230 (CH aromatic), 2983(CH aliphatic), 2189(C≡N), 1728 (C=O ester), 1684 (C=O cyclic amide), 1642 (C=N), 832 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 7.47-7.14 (m, 4H, Ar-H), 6.99 (s, 2H, D_2O-exchangeable, NH_2), 6.82 (s, 1H, thiazine moiety), 5.70 (s, 1H, benzylic proton), 4.26 (q, 2H, *J* = 7.5 Hz, -$\underline{CH_2}CH_3$), 1.22 (t, 3H, *J* = 7.5 Hz, -$CH_2\underline{CH_3}$). MS (m/z(%)): 390 (M+2] $^{\bullet+}$, 93), 389 (M+1] $^{\bullet+}$ 83), 370 (79), 355 (70), 346 (69), 300 (86), 256 (84), 203 (64), 173 (96) and 50 (100).

6-(4-Chlorophenyl)-4-(ethylamino)-2-(ethylthio)-1,6-dihydropyrimidine-5-carbonitrile (15)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), ethyl iodide (0.47 g, 10 mmol) in sodium ethoxide (0.23 g, 10 mmol of sodium in 30 ml of dry ethanol) was refluxed for 4 h. The reaction mixture was cooled, then poured onto ice/water and the separated solid was crystallized from ethanol to afford **15** as white crystals, mp 199-200 °C, yield **79 %**. FT-IR (KBr, cm^{-1}): 3367, 3341 (NH), 3042 (CH aromatic), 2245 (C≡N), 1682 (C=N), 832 ($\delta_{2\text{-}H}$).^{1}H-NMR (DMSO-d_6, 300 MHz): 8.30 (s, 1H, D_2O-exchangeable, NH), 7.65 (s, 1H, D_2O-exchangeable, NH), 7.45 (d, 2H, *J* = 6.3Hz, Ar-H), 7.22 (d, 2H, *J* = 6.3Hz, Ar-H), 4.96 (s, 1H, benzylic proton), 2.81 (q, 2H, *J* = 6.3Hz, -S$\underline{CH_2}CH_3$), 1.92 (q, 2H, *J* = 7.2Hz, -N$\underline{CH_2}CH_3$), 1.77 (t, 3H, *J* = 6.3Hz, -$CH_2\underline{CH_3}$) and 1.09 (t, 3H, *J* = 7.2Hz, -$NCH_2\underline{CH_3}$). MS (m/z(%)): 322 (M+2] $^{\bullet+}$, 17), 321 (M+1] $^{\bullet+}$, 11), 320 (M] $^{\bullet+}$,40), 291 (40), 185 (34), 165 (53), 140 (100), 111 (15) and 88 (39).

4-Amino-6-(4-chlorophenyl)-2-(ethylthio)-1,6-dihydropyrimidine-5-carbonitrile (16)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), ethyl iodide (0.47 ml, 10 mmol), fused sodium acetate (0.62 g, 15 mmol) in dry ethanol (30 ml) was refluxed for 10 h. The reaction mixture was cooled, then poured onto ice/water and recrystallized from toluene to afford **16** as white crystals, mp 170-172 ºC, yield 78%. FT-IR (KBr, cm^{-1}): 3376, 3315 (NH_2), 3181 (CH aromatic), 2962 (CH aliphatic), 2211 (C≡N), 1651 (C=N), 851 ($\delta_{2\text{-}H}$).^{1}H-NMR (DMSO-d_6, 300 MHz): 8.10 (s, 2H, D_2O-exchangeable, NH_2), 7.86 (d, 2H, *J* = 8.7Hz, Ar-H), 7.64 (d, 2H, *J* = 8.7Hz, Ar-H), 3.11 (q, 2H, *J* = 7.5 Hz, -S$\underline{CH_2}CH_3$) and 1.31 (t, 3H, *J* = 7.5Hz, -$CH_2\underline{CH_3}$). MS (m/z(%)): 292 (M+2] $^{\bullet+}$, 44), 291 (M+1] $^{\bullet+}$, 32), 290 (M] $^{\bullet+}$, 86), 275 (86), 257 (100), 229 (72), 195 (46), 176 (26), 149 (40), 111 (32) and 73 (64).

Ethyl 2-(4-amino-6-(4-chlorophenyl)-5-cyanopyrimidin-2-ylthio)acetate (17)

A mixture of tetrahydropyrimidine **4** (1.3 g, 10 mmol), ethyl chloroacetate (0.56 ml, 10 mmol), fused sodium acetate (0.62 g, 15 mmol) in dry ethanol (30 ml) was refluxed for 14 h. The reaction mixture was cooled, then poured onto ice/water then collected by filtration, washed with water and recrystallized from ethanol to afford **17** as brown crystals, mp 244-250 ºC, yield 72%. FT-IR (KBr, cm^{-1}): 3355, 3320, (NH_2), 3176 (CH aromatic), 2975 (CH aliphatic), 2218 (C≡N), 1739 (C=O ester), 1659 (C=N), 854 ($\delta_{2\text{-}H}$).^{1}H-NMR (DMSO-d_6, 300 MHz): 9.48, 9.21 (2 s, 2H, D_2O-exchangeable, 2NH), 7.66 (2 dd, 4H, *J*= 6.9 and 2.1 Hz, Ar-H), 4.11 (q, 2H, *J* = 7.2 Hz, -O$\underline{CH_2}CH_3$), 4.02 (s, 2H, -S-$\underline{CH_2}$-COO) and 1.14 (t, 3H, *J* = 7.2Hz, -$OCH_2\underline{CH_3}$). MS (m/z(%)): 350 (M+2] $^{\bullet+}$, 32), 349 (M+1] $^{\bullet+}$, 32), 348 (M] $^{\bullet+}$, 35), 322 (38), 312 (38), 300 (35), 241 (41), 190 (33) and 69 (100).

4-Amino-6-(4-chlorophenyl)-2-hydrazinylpyrimidine-5-carbonitrile (18)

A mixture of enaminonitrile **16** (1.46 g, 10 mmol), hydrazine hydrate (98%) (0.67 ml, 12 mmol) in boiling ethanol (30 ml) was refluxed for 4 h. The solid product was collected by filtration, dried and recrystallised from ethanol to afford **18** as white crystals, mp 284-285 °C, yield 84%. FT-IR (KBr, cm^{-1}): 3413, 3344, 3252 (NH_2& NH), 3062 (CH aromatic), 2214 (C≡N), 1659 (C=N), 833 ($\delta_{2\text{-}H}$) .^{1}H-NMR (DMSO-d_6, 300 MHz): 8.71 (s, 1H, D_2O-exchangeable, NH), 7.82-7.56 (m, 4H, Ar-H), 7.25 (s, 2H, D_2O-exchangeable, NH_2) and 4.35 (s, 2H, D_2O-exchangeable, NH_2). MS (m/z(%)): 262 (M+2)$^{\cdot+}$, 43), 260 (M$^{\cdot+}$, 75), 245 (35), 231 (46), 203 (47), 148 (47), 138 (52) and 75(100).

5,7-Diamino-9-(4-chlorophenyl)-3-(4-methoxyphenyl)pyrimido[2,1-c][1,2,4]triazepine-4,8-dicarbonitrile (19)

A mixture of enaminonitrile **18** (1.3 g, 10 mmol) and 2-(4-methoxybenzylidene)malononitrile (0.9 g, 10 mmol) in (10 ml) of DMF (dimemthylformamide) was refluxed for 14 h. The reaction mixture was poured into ice cold water, filtered and recrystallized from ethanol to afford **19** as brown crystals, mp 291-293 °C, yield 84%. FT-IR (KBr, cm^{-1}): 3466, 3291, 3155 (NH_2), 3113 (CH aromatic), 2965(CH aliphatic), 2203 (C≡N), 1649 (C=N), 830 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 11.27 (s, 1H, D_2O-exchangeable, NH_2), 8.23-6.98 (m, 10H, Ar-H, D_2O-exchangeable, NH_2) and 3.82 (s, 3H, -OCH_3). MS (m/z(%)): 444 (M+2)$^{\cdot+}$, 1), 442 (M$^{\cdot+}$, 3), 378 (3), 247 (32), 245 (100), 244 (40) and 203 (23).

N-(4-Amino-6-(4-chlorophenyl)-5-cyanopyrimidin-2-yl)formamide (20)

A mixture of enaminonitrile **16** (1.46 g, 10 mmol) in boiling formamide (10 ml) was refluxed for 18 h. Left to cool, the reaction mixture was poured into ice/water. The precipitated solid was filtered, washed with water and recrystallized from methanol to give **20** as yellow crystals, mp 278-280 °C, yield 85 %. FT-IR (KBr, cm^{-1}): 3427, 3375 (NH_2), 3148 (CH aromatic), 2205 (C≡N), 1683 (C=O), 1616 (C=N), 836 ($\delta_{2\text{-}H}$). ^{1}H-NMR (DMSO-d_6, 300 MHz): 10.98 (s, 1H, D_2O-exchangeable, NH), 9.49 (s, 1H, -NH-CHO), 7.82-7.39 (m, 4H, Ar-H) and 7.18 (s, 2H, D_2O-exchangeable, NH_2). MS (m/z(%)): 275 (M+2)$^{\cdot+}$, 50), 266 (60), 246 (60), 204 (72), 159 (60), 125 (63), 102 (70), 81 (80) and 57 (100).

N-(6-(4-Chlorophenyl)-5-cyanopyrimidin-4-yl)formamide (21)

A solution of enaminonitrile **16** (1.46 g, 10 mmol) in formic acid (10 ml) was refluxed for 27 h. Left to cool, then poured into ice/water. The precipitated solid was filtered, washed with water and recrystallized from ethanol to afford **21** as white crystals, mp 257-259 °C, yields72 %. FT-IR (KBr, cm^{-1}): 3576 (NH non-bonded), 3135 (NH bonded), [36] 2209 (C≡N), 1645 (C=O formyl), 840 ($\delta_{2\text{-}H}$).^{1}H-NMR (DMSO-d_6, 300 MHz): 10.11 (s, 1H, D_2O-exchangeable, NH) and 7.72-7.48 (m, 6H, 4Ar-H, =CH pyrimidine moiety & O=CH). MS (m/z(%)): 258 (M)$^{\cdot+}$, missed), 229 (7), 219 (9), 204 (13), 138 (100), 111 (41) and 80 (76).

Determination of Total Antioxidant Capacity (TAC)

The antioxidant activity (AOA) of each compound was determined according to phosphomolybdenum method [37] using ascorbic acid as standard. This assay is based on the reduction of Mo (VI) to Mo (V) by the sample analyte and subsequent formation of a green colored [phosphate=Mo (V)] complex at acidic pH. In this method, 0.5 ml of each compound (100 µg /ml) in methanol was combined in dried vials with 5 ml of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The vials containing the reaction mixture were capped and incubated in a thermal block at 95°C for 90 min. After the samples had cooled at room temperature, the absorbance was measured at 695 nm against a blank. The blank consisted of all reagents and solvents without the sample and it was incubated under the same conditions. All experiments were carried out in triplicate. The antioxidant activity of the sample was expressed as the number of ascorbic acid equivalent (AAE). The phosphomolybdenum assay is based on the reduction of Mo^{VI} to

Mo^V by antioxidant compounds and the formation of a green phosphate/Mo^V complex with a maximal absorption at 695 nm.

CONCLUSION

A variety of fused and non fused heterocyclic systems containing pyrimidine nucleus have been synthesized from the reaction of arylidines with different nucleophiles. All the synthesized pyrimidines are potent antioxidants. In particular the hydrazinylpyrimidine **8**, dihydropyrimido[4,5-d]pyrimidine **11** and pyrimidine-5-carbonitrile **16** showed the most antioxidant activity (AOA) expressed in 562.0 ± 5.03, 449.96 ± 1.20 and 506.66 ± 4.05 mg AAE /g compound(AAE= Ascorbic Acid Equivalent) using ascorbic acid as standard.

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REFERENCE

[1]. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, R. P. Mai, R. K. Johnson, J. W.Westley and B. C. M. Potts, Novel Alkaloids from the Sponge Batzella sp.: Inhibitors of HIV gp120-Human CD4 Binding, *J. Org. Chem.*, Vol. 60, pp.1182-1188, 1995.

[2]. S. Rajasekaran, G. K. Rao, P. P. N. Sanjay and A. K. Ajay, Design, Synthesis and Biological Activity of Substituted Dihydropyrimidine-2-(1H)-thiones, *Int. J. Pharm. Tech. Research*, Vol. 3(2), pp. 626-631, 2011.

[3]. S. Chitra, D. Devanathan and K. Pandiarajan, Synthesis and *in-vitro* microbiological evaluation of novel 4-aryl-5-isopropoxycarbonyl-6-methyl-3,4-dihydropyrimidinones, *Eur. J. Med. Chem.*, Vol. 45, pp. 1-5, 2009.

[4]. M. B. Deshmukh, S. M. Salunkhe, D. R. Patil and P. V. Anbhule, A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines and their anti-bacterial activity, *Eur. J. Med. Chem.*, Vol. 44, pp.2651-2654, 2009.

[5]. C. O. Kappe, Biologically active dihydropyrimidones of the Biginelli-type- a literature survey, *Eur. J. Med. Chem.*, Vol. 3, pp.1043-1052, 2000.

[6]. S. M. Sondhi, S. Jain, M. Dinodia, R. Shukla and R. Raghubir, One pot synthesis of pyrimidine and bispyrimidine derivatives and their evaluation for anti-inflammatory and analgesic activities *Bioorg. Med. Chem.*, Vol.15, pp. 3334-3344, 2007.

[7]. R. V. Chikhale, R. P. Bhole, P. B. Khedekar and K. P. Bhusari, Synthesis and pharmacological investigation of 3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates, *Eur. J. Med. Chem.*, Vol. 44, pp. 3645-3653,2009.

[8]. R. Sawant and V. Sarode, Synthesis, Spectral Characterization and Analgesic Activity of 2-Methylthio-1,4-Dihydropyrimidines, *Iranian J. Pharm. Res.*, Vol. 10 (4), pp.733-739, 2011.

[9]. A. Balkan, M. Ertan and T. Burgemeister, Synthesis and structural evaluations of thiazolo[3,2-a]pyrimidine derivatives, *Arch Pharm (Weinheim)*, Vol. 325, pp. 499-501, 1992.

[10]. I. S. Zorkun, S. Sarac, S. C. Elebib and K. Erol, Synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-thione derivatives as potential calcium channel blockers, *Bioorg. Med. Chem. Lett.*, Vol. 14, pp. 8582-8589, 2006.

[11]. G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland and J. Z. Gougoutas, Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-

aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents, *J. Med. Chem.*, Vol. 35, pp. 3254-3263,1992.

[12]. L. Ismaili, A. Nadaradjane, L. Nicod, C. Guyon and A. Xicluna, Synthesis and antioxidant activity evaluation of new hexahydropyrimido[5,4-c]quinoline-2,5-diones and 2-thioxohexahydropyrimido[5, 4-c]quinoline-5-ones obtained by Biginelli reaction in two steps, *Eur. J. Med. Chem.*, Vol. 43, pp. 1270-1275, 2008.

[13]. S. M. Sondhi, M. Dinodia, R. Rani, R. Shukla and R. Raghubir, Synthesis, anti-inflammatory and analgesic activity evaluation of some pyrimidine derivatives, *Ind. J. Chem.*, Vol. 49b, pp. 273-281, 2009.

[14]. M. S. Mohamed, S. M. Awad, Y. M. Zohny and Z. M. Mohamed, New Theopyrimidine Derivatives of Expected Anti-inflammatory Activity, *Pharmacophore*, Vol. 3 (1), pp. 62, 2012.

[15]. A. Mohammad, A. J. Sadique and K. Harish, Synthesis and biological evaluation of some 4-(1*H*-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-ones/thiones as potent anti-inflammatory agents, *Acta Pharm*, Vol. 58, pp. 467-7-477, 2008.

[16]. D. S. Bose, M. Sudharshan and S.W. Chavhan, New protocol for Biginelli reaction a practical synthesis of Monastrol, *Arkivoc*, pp. 228-236, 2005.

[17]. Y. P. He, J. Long, S. S. Zhang, C. Li, C. C. Lai, C. S. Zhang, D. X. Li, D. H. Zhang, H. Wanga, Q. Q. Cai and Y. T. Zheng, Synthesis and biological evaluation of novel dihydro-aryl/alkylsulfanylcyclohexylmethyl-oxopyrimidines (S-DACOs) as high active anti-HIV agents *Bioorg. Med. Chem. Lett.* Vol. 21, pp. 694-697, 2011.

[18]. Y. He, F. Chen, G. Sun, Y. Wang, E. D. Clercq, J. Balzarini and C. Pannecouque, Alkyl-2-[(aryl and alkyloxylcarbonylmethyl)thio]-6-(1-naphthylmethyl)pyri-midin-4(3*H*)-ones as an unique HIV reverse transcriptase inhibitors of S-DABO series, *Bioorg. Med. Chem. Lett.* Vol.14, pp. 3173-3176, 2004.

[19]. D. Russowsky, R. F. S. Canto, S. A. A. Sanches, M. G. M. D'Oca, A. D. Fatima and J. E. D. Carvalho, Synthesis and differential antiproliferative activity of Biginelli compounds against cancer cell lines: Monastrol, oxo-monastrol and oxygenated analogues, *Bioorg. Chem.*, Vol. 34, 173-182, 2006.

[20]. M. R. Mahmoud, H. M. F. Madkour, M. M. Habashy and A. M. El-Shwaf, Heteroannulation of Pyrido[2,3-d]Pyrimidines. Synthesis and Spectral Characterization of Pyridotriazolopyrimidines, Pyrido pyrimidotriazine and pyridopyrimidotriazepine Derivatives, *Amer. J. Org. Chem.*, Vol. 2 (1), pp. 39-47, 2012.

[21]. H. M. F. Madkour, A. A. E. Afify, A. A. Abdallaha, G. A. Elsayed and M. S. Salem, Synthetic Utility of Enaminoester Moiety in Heterocyclic Synthesis", *European Journal of Chemistry*, *Eur. J. Chem.*, Vol. 1 (4), pp. 352-359, 2010.

[22]. H. M. F. Madkour, M. E. Azab and M. A. E. Ibraheem, 5,6,7,8-Tetrahydrobenzo[b]thieno[2,3-d]pyrimidine-4(3H)one as a Synthon of Heterocyclic Systems, *Bulg. Chem. Comm.*, Vol. 41(1), pp. 12-18, 2009.

[23]. H. M. F. Madkour, A. A. E. Afify, A. A. Abdalha, G. A. Elsayed and M. S. Salem, Synthetic Utility of Enaminonitrile Moiety in Heterocyclic Synthesis: Synthesis of Some New Thienopyrimidines, *Phosphorus, Sulfur, and Silicon and the Related Elements*, Vol. 184, pp. 719-732, 2009.

[24]. M. A. I. Salem, H. M. F. Madkour, M. I. Marzouk, M. E. Azab and N. F. H. Mahmoud, Pyrimidinthiones (Part I): Utility of 2-Thioxopyrimidin-6-(1H)ones as Ring Transformer in the Synthesis of Fused Bi- and Tri-Cyclic Heterocyclic Compounds and Their Potential Biological Activities, *Phosphorus, Sulfur, and Silicon and the Related Elements*, Vol.183, pp. 2596-2614, 2008.

[25]. K. A. Kandeel, The Behaviour of *E,Z*-5-Arylmethylidene-2-thioxo-1,3-thiazolidin-4-

one and 3-[(2-Oxo-2H-1-benzopyran-3-yl)dithio]-2H-1-benzopyran-2-one Derivatives towards Some Amines, *Chem. Pap.*, Vol. 58(5), pp. 334-340, 2004.

[26]. M. Ware, B. Madje, R. Pokalwar, G. Kakade and M. Shingare, DBU: An efficient catalyst for Knoevenagel condensation under solventfree condition, *Bulletin of the Catalysis Society of India* ,Vol. 6, pp. 104-106, 2007.

[27]. S. Kambe and K. Saito, A. Sakurai, H. Midorikawa, Synthetic Studies Using α,β-Unsaturated Nitriles: Facile Synthesis of Pyridine Derivatives, *Synthesis*, pp.531-533,1981.

[28]. N. Baummann, M. Sung and E. F. Uliman, Wavelength-dependent photochemical reactions of lactones, *J. Amer. Chem. Soc.*, Vol. 90(15), pp. 4157-4158, 1968.

[29]. R. L. Autrey and F. C. Talk, The synthesis and stereochemistry of some isatylideneacetic acid derivatives, *Tetrahedron* Vol. 23, pp.901-917, 1970.

[30]. R. W. Daisley and J. Walker, Substituted oxindoles. Part V. Synthesis and stereochemistry of some substituted 3-benzylidene-1-methylindol-2(3*H*)-ones, *J. Chem. Soc. (C)* pp.3357-3363, 1971.

[31]. G. Desmoni, A. Gamba and R. P. P. Tacconi, *Gazz. Chim. Ital.*, Vol. 102, pp. 491, 1972.

[32]. D. R. Patil, S. M. Salunkhe, M. B. Deshmukh and P. V. Anbhule, One Step Synthesis of 6-Amino-5-Cyano-4-Phenyl-2-Mercapto Pyrimidine Using Phosphorus Pentoxide, *The Open Catalysis Journal*, Vol. 3, pp.83-86, 2010.

[33]. P. K. Chaudhari, Synthesis and Biological Studies of TrihydroPyrido[2,3-D]Pyrimidines-6-Carbonitrile, *Inter. J. Life Science & Pharma Research*, Vol. 1 (1), pp. L71-L76, 2011.

[34]. S. Kambe, K. Saito, A New, Convenient synthesis of 7H-Thiazolo[3,2-a]pyridine Derivatives from α-Cyanocinnamic Esters and Mercaptoacetic Ester, *Synthesis*, pp. 839, 1977.

[35]. X. L. Li, Y. M. Wang, B. Tian, T. Matsuura and J. B. Meng, The solid-state Michael addition of 3-methyl-1-phenyl-5-pyrazolone, *J. Heterocycl. Chem.*, Vol. 35 (1), pp. 129-134, 1998.

[36]. J. R. Dyer, Application of Absorption Spectroscopy of organic compounds, Prentice-Hall of india Private Limited, New Delhi-110001, pp. 114 & 36,1978.

[37]. P. Prieto, M. Pineda and M. Aguilar, Spectrophotometric Quantitation of Antioxidant Capacity through the Formation of a Phosphomolybdenum Complex: Specific Application to the Determination of Vitamin E, *Anal. Biochem.*, Vol. 269, pp. 337- 341,1999.