Science Journal of Chemistry
2013; 1(1): 1-6
Published online April 2, 2013 (http://www.sciencepublishinggroup.com/j/sjc)
doi: 10.11648/j.sjc.20130101.11

Green and efficient synthesis of some pyrido [2,3-d]pyrimidin-4(3h)-one derivatives via iodine catalyst in aqueous media and evaluation the synthesized compounds as anticancer

Ayman M. F. Elgohary[1,2,*], E. M. Ezz El-Arab[2]

[1]Department of medical laboratories College of Applied Medical Science, Majmaah University, Almajma'ah 11952, KSA
[2]National Organization For Drug Control & Research, Pharmaceutical Chemistry Division, Giza, Egypt

Email address:
Elgohary431974@yahoo.com (A. M. F. Elgohary)

To cite this article:
Ayman M. F. Elgohary, E. M. Ezz El-Arab. Green and Efficient Synthesis of Some Pyrido[2,3-D]Pyrimidin-4(3h)-One Derivatives Via Iodine Catalyst in Aqueous Media and Evaluation the Synthesized Compounds as Anticancer, *Science Journal of Chemistry*. Vol. 1, No. 1, 2013, pp. 1-6. doi: 10.11648/j.sjc.20130101.11

Abstract: A series of new 2-propylpyrido[2,3-d]pyrimidin-4(3H)-one with different substituents at position 3 were synthesized by traditional method and Iodine catalyst method. The effect of the newly synthesized compounds was tested as anti-cancer in National Cancer Institute(NCI)in USA. Some of the synthesized compounds exploited potent antitumor activity, especially the compounds pyrido[2,3-d][1,3]oxazin (2), 3-amino derivative 3a, 3b and hydroxy derivative 3c displayed the highest activity among the test compounds with IC50 < 5 mg/mL

Keywords: Pyrido[2,3-D][1,3]Oxazin-4-One, 2-Propylpyrido[2,3-D]Pyrimidin-4(3h)-One, Antitumor

1. Introduction

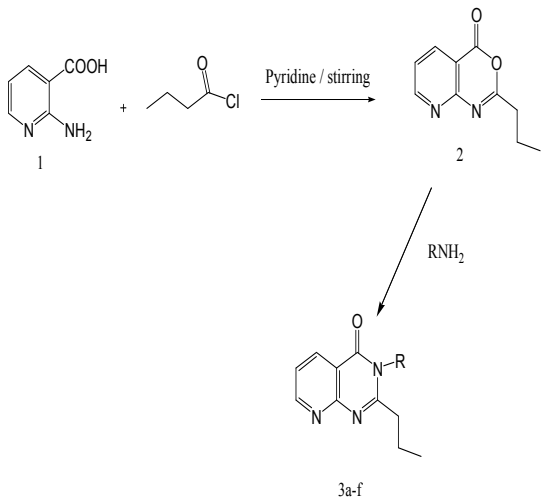
Cancer is the second leading cause of death in the world. The pyrido[2,3-d]pyrimidine nucleus represents in many biologically active compounds which includes antitumour [1-7], antibacterial [8], anticonvulsant [9], antipyretic [10], analgesic [11], and CNS depressant activity [12]. Specifically pyrido[2,3-d]pyrimidines known to inhibit Pneumocystis carinii(pc), Toxoplasma gondii(tg) of tumor cell lines in culture [13] and the activity is attributed to inhibition of dihydrofolate reductase (DHFR) [14,15]. In modern synthetic organic chemistry, development of a novel and efficient method for synthesis of pyridopyrimidine and its biological activity is one of the current areas of research interest. In this work, we aimed to synthesize new 2-propylpyrido[2,3-d]pyrimidin-4(3H)-one derivatives bearing different substituents at position 3 [NH_2, N-aryl] in order to, examine the effect of substitution at position 3 on the antitumor activity.

2. Result and Discussion

2-propyl- 4H- pyrido [2,3-d] [1,3] oxazin- 4- one (2) has been synthesized from the interaction of butyroyl chloride with 2-aminonicotinic acid in pyridine to give 2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (2). The structure of compound 2 was inferred from its IR spectra (cm^{-1}) which exhibits strong absorption bands at 1614, 1764 (cm^{-1}) due to υ_{max}.of C=N and C=O of pyridoxazinone and lack of any band for NH and / or OH. The starting compound 3a was prepared via reacting pyridooxazinone (2) with hydrazine hydrate in ethanol in water path, the formation of compound 3a was confirmed by ^{1}HNMR that showed singlet signal at □ 9.8ppm and from its IR spectrum which exhibits strong absorption bands at 1614 and 1670 (cm^{-1}) due to υ_{max}. of C=N, C=O and lack of any band for of C=O of pyridoxazinone, also compound 2 was reacted with ammonium acetate in an oil bath to form 2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3b). Beside the same compound 3b was obtained by heating compound 2 in formamide under reflux. On a reaction of compound 2 with hydroxyl amine gave 3-hydroxy-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3c).

On the other hand compounds 3d-f were prepared by interaction of compound 2 with aromatic amines namely orth, meta and para toluidine. The structure of compounds 3d-f were inferred from its IR spectrum which exhibits strong absorption bands at 1614 and 1670 (cm^{-1}) due to υ_{max}. of

C=N, C=O and lack of any band for of C=O of pyridoxazinone.



Scheme 1

Table 1. *Synthesis of 2-propylpyrido[2,3-d]pyrimidin-4(3H)-one and its derivatives 3a-c.*

Comb. No.	R	Molecular formula M.wt	Reagent and condition	Time (h)	mp (°C)
3a	NH_2	$C_{10}H_{12}N_4O$ 204	NH_2NH_2/ EtOH	0.5	130
3b	H	$C_{10}H_{11}N_3O$ 189	formamide	3	286
	H	$C_{10}H_{11}N_3O$ 189	CH_3COONH_4 oil bath / 150 °C	3	286
3c	OH	$C_{10}H_{11}N_3O_2$ 205	NH_2OH/ EtOH reflux	3	165
3d		$C_{17}H_{17}N_3O$ 279	EtOH reflux	4.5	234
3e		$C_{17}H_{17}N_3O$ 279	EtOH reflux	5	255
3f		$C_{17}H_{17}N_3O$ 279	EtOH reflux	5	195

On the other hand Three methods were investigated for the synthesis of 3-(Arylylideneamino)-2- propylpyrido [2,3-d]pyrimidin-4(3H)-ones 4a-k, the first is method A (traditional method) by condensation of 3- amino- 2-propylpyrido[2,3-d] pyrimidin-4(3H)-one (3b) and aryl aldehydes in refluxing ethanol but this methods suffering from high temperature, low yield, long reaction time. As part of our interests in the synthesis of pyridopyrimidine and due to the present awareness of applying environmentally benign strategies in organic synthesis, in this communication we report the I2/KI mediated condensation of 3-amino- 2- propylpyrido [2,3-d] pyrimidin- 4(3H) -one (3a) with various aldehydes for preparation of 3 -(Arylylideneamino) - 2- propylpyrido [2,3-d] pyrimidin - 4(3H)- ones 4a-k in ethanol–water (method B) or boiling water (method C).

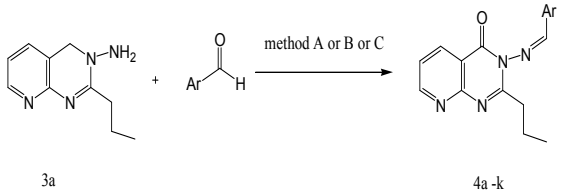
Initially, a solution of I_2/KI was prepared by dissolving specified molecular iodine in a saturated aqueous solution of potassium iodide. We were delighted to find that expo sure of 3-amino-2-propylpyrido [2,3-d] pyrimidin - 4(3H) - one (3a) with aromatic aldehydes on stirring or refluxing in equimolar aqueous solution of I_2/KI offered the 3-(Arylylideneamino) - 2- propylpyrido [2,3-d] pyrimidin-4(3H)-ones 4a-k in good to excellent isolated yields (Scheme 2).

To assess the catalytic effect of I_2/KI system, the typical reaction of 3- amino -2- propylpyrido [2,3-d] pyrimidin-4(3H)-one (3a) with benzaldehyde was attempted in the absence of I_2/KI catalyst at room temperature and also at reflux temperature, but only the starting materials were recovered. It can be assumed that in the I_2/KI catalytic system, molecular iodine acts as a mild Lewis acid and oxidant and KI as a solubilizing agent of molecular iodine in water. On the other hand water as the reaction media is mostly suitable because the products are practically insoluble in water and the work-up process can be much simplified. The reaction was performed in two methods. In method (B), reactants were first dissolved in minimum ethanol (ca. 1 mL) in order to make the mixture homogeneous then, the I_2/KI aqueous solution was added and stirred at room temperature for desired times indicated in Table 2. Progress of the reaction was monitored by TLC. In method (C), the reaction was only conducted in I_2/KI aqueous solution at reflux conditions. The products from both procedures were isolated in a practically pure form by simple Buchner filtration of the final aqueous mixture. The structures of these compounds were established by their physical and spectral data (Table 2).

From the data in table (2) it can be concluded that the presence of the electron-withdrawing substituents on the aromatic ring like entry 4c and 4d can increase the reaction rate and as the result the reaction times are shortened and the yields are increased while the electron donating substituents have the diverse effect. It should be pointed out here that yields from method (B) are higher compared with that of method (C) and yields from method (C) are higher compared with that of method (A). But the reactions in method (C) showed an attractive feature from the viewpoint of environmental benign.

Table 2. *Synthesis of 3-(Arylylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-ones 4a-k.*

Entry	Ar	Molecular formula	Method A Traditional method		Method B I_2/KI in Ethanol/ water		Method C I_2/KI in Water		mp (^oC)
			Yield %	Time (h)	Yield %	Time (min)	Yield %	Time(min)	
4a		$C_{17}H_{16}N_4O$ 292	80	4	91	25	85	40	233
4b		$C_{18}H_{18}N_4O$ 308	73	6	93	35	82	45	238
4c		$C_{17}H_{15}N_4OCl$ 262.5	80	5	95	20	89	60	302
4d		$C_{17}H_{15}N_5O_3$ 337	75	3.5	92	15	87	45	315
4e		$C_{17}H_{15}N_5O_3$ 337	60	4	95	30	83	50	305
4f		$C_{18}H_{18}N_4O_2$ 322	74	5	83	45	78	60	216
4g		$C_{18}H_{18}N_4O_2$ 322	77	7	94	30	80	60	226
4h		$C_{18}H_{18}N_4O_2$ 322	82	6	91	30	84	90	219
4i		$C_{17}H_{16}N_4O_2$ 310	75	5	97	30	82	120	254
4j		$C_{17}H_{16}N_4O_2$ 310	70	5	87	35	80	120	266
4k		$C_{17}H_{16}N_4O_2$ 310	72	6	90	30	83	90	245



Scheme 2

3. Biological Part

The Development Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) USA has used an In-vitro model consisting of 60 human tumor cell lines as the primary anticancer screen. An analysis of the data indicated that approximately 95% of the actives from the 60-cell line screen could be identified using only three cell lines. For this reason, the DTP has begun using, as its primary anti-cancer assay, a 3-cell lines panel consisting of NCI-H 460(Lung), MCF7 (Breast), and SF-268 (CNS). The NCI protocol has been described previously briefly. Cell lines were inoculated onto a series of 96-well plates. Seeding densities varied depending upon growth characteristics. After a 24h – drug - free incubation, test compounds were added routinely at five tenfold dilutions starting at maximum 10-4M. After incubation periods of 48h or 6 days, cell growth or viability was assayed using the sulphorhodamine B procedure42.The results of antineoplastic evaluation of the tested compounds it is evident that the all compounds showed cytotoxic effects and high selectivity against breast adenocarcenoma (MCF7), Doxorubicin which is one of the most effective anticancer agents was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line (MCF7). The response parameter calculated was the IC50 value, which corresponds to the concentration required for 50% inhibition of cell viability. The IC50 of the synthesized compounds compared to the reference drug are shown in Table 4. From the results in Table (3), it was found that the best results were obtained by compounds pyrido[2,3-d][1,3]oxazin (2), 3-amino derivative 3a, 3b and hydroxy derivative 3c. Regarding the chloro 4c and hydroxyl substituted 4i-k give moderate activity. Compound 3b was the most potent com-

pound in this screening with IC50 equal to 3.82 mg/mL.. Further studies needed to be done to explore the mechanism of action as well as the effect of substitution at other positions of the ring.

Table 3. *Results of in vitro cytotoxic activity of the synthesized compounds on human breast adenocarcinoma cell line (MCF7).*

Compound no.	IC50 in mg/mL
2	4.21
3a	4.93
3b	3.82
3c	4.77
3d	14.58
3e	33.98
3f	29.22
4a	17.46
4b	20.5
4c	11.12
4d	> 50
4e	> 50
4f	15.6
4g	11.23
4h	10.29
4i	12.46
4j	9.33
4k	11.65
Doxorubicin	3.11

3. Conclusion

The objective of the present study was to synthesize new pyrido [2,3-d]pyrimidinones by different method bearing different substituents at position 3 and to examine the effect of substitution at position 3 on the cytotoxic activity. Some of these new compounds exhibited good antitumor activity against MCF7 when compared to doxorubicin as a reference drug. The best results were obtained by derivatives bearing NH_2, OH or NH groups at position 3. The 3-amino derivative 3a was the most potent compound in this screening with IC50 equal to 3.82 mg/mL.

4. Experimental

All melting point are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. Microanalysis were carried out by the Micro Analytical Unit at Cairo University. IR spectra (KBr disk) were recorded on FT/IR-300E Jasco spectrophotometer. HNMR spectra were recorded in CDCl3 or DMSO-d6 solution on a Varian EM 390-90 MHz43,44. Mass spectrometry were recorded were recorded Shomadzu, GC – MS (QP – 1000EX

2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (2)

A stirred solution of 2-aminonicotinic acid 13.8g (0.1 mol) in dry pyridine (150 ml) was treated drop wise with n-butyroyl chloride 10.5g (0.11 mol) during 10 min. the mixture was stirred at room temperature (3hours) and poured into a mixture of ice and hydrochloric acid gave crude 2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one The precipitated solid was filtered off , washed with cold water and recrystallization from petroleum ether 40 – 60 oC, giving 2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (2) as a colorless crystals melting point(63 oC) (2) IR(KBr) cm-1: 3055 (CH aromatic), 2965, 2935, 2875 (CH aliphatic),1764(C=O), 1614(C=N),1161 (C-O) ; MS: m/z 190 [M+]; Anal. calcd. for C10H10N2O2 : C, 63.15; H, 5.26; N, 14.73; found: C, 63.11; H, 5.24; N, 14.70

3-amino-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3a)

Compound (2) (1.89 g- 10mmol) and 5 ml hydrazine hydrate were heated in water bath for 1/2 hour and then added 50ml ethanol the mixture was refluxed, The completion of the reaction was monitored by TLC using chloroform: methanol (8:2) as eluent and the obtained solid was filtered off and recrystalization from petroleum ether 60- 80 ^oC to give 3-amino-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3a). IR(KBr) cm^{-1} : 1596(C=N), 1673(C=O), 2875, 2935,2965 (CH aliphatic), 3055 (CH aromatic), 3309, 3212(NH_2); MS: m/z 204 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 9.8 (s, 2H, NH_2), 7.6 – 8.8 (m, 3H, aromatic), 2.7 (t,2H, CH_2pyrimidine), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{10}H_{12}N_4O$: C, 58.82; H, 5.88; N, 27.45; found: C, 58.80; H, 5.84; N, 27.41.

2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3b)

method A- 2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (2) (1mmol) was heated with ammonium acetate (4mmol) in an oil bath at 150 ^oC for two hours, the reaction mixture was cooled and poured in cold water. The precipitated solid was filtered off , washed with water and recrystallization from ethanol to give 3b. IR(KBr) cm^{-1} : 3215 (NH), 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 189 [M^+]; ^{1}HNMR (DMSO) : δ 8.9 (s, H, NH), 7.2 – 8.2 (m, 3H, aromatic), 1.1(t, 3H, CH_3), 1.9 (sextet,2H,CH_2Me), 2.7 (t,2H, CH_2); Anal. calcd. for $C_{10}H_{11}N_3O$: C, 63.49; H, 5.82; N, 22.22; found: $C_{10}H_{11}N_3O$: C, 63.45; H, 5.79; N, 22.20

method B- 2-propyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (2) (1mmol) in formamide (20 ml) was refluxed for 3 hours, the reaction mixture was cooled and poured in cold water. The obtained solid was filtered off and recrystalized from the proper solvent IR(KBr) cm^{-1} : 3215 (NH), 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 189 [M^+]; ^{1}HNMR (DMSO) : δ 8.9 (s, H, NH), 7.2 – 8.2 (m, 3H, aromatic), 1.1(t, 3H, CH_3), 1.9 (sextet,2H,CH_2Me), 2.7 (t,2H, CH_2); Anal. calcd. for $C_{10}H_{11}N_3O$: C, 63.49; H, 5.82; N, 22.22; found: $C_{10}H_{11}N_3O$: C, 63.45; H, 5.79; N, 22.20

3-hydroxy-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3c)

A solution of compound (2) (10mmol) and hydroxylamine hydrochloride in boiling ethanol (25 ml) was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was cooled and crystallized from the proper solvent to afford 3c. IR(KBr) cm^{-1} : 3435 (OH), 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1676 (C=O), 1573(C=N) ; MS: m/z 205 [M^+]; ^{1}HNMR (DMSO) : δ 9.7 (s, H, OH), 7.2 – 8.2 (m, 3H, aromatic), 1.1(t, 3H, CH_3), 1.9 (sextet,2H,CH_2Me), 2.7

(t,2H, CH_2); Anal. calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36; N, 20.48; found: C, 58.51; H, 5.32; N, 20.44.

3-(arylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one 3d-f

General procedure: a mixture of compound 2 (10 mmol) and aromatic amines (10mmol) namely p-toluidine o-toluidine and, or m-toluidine in 50 ml ethanol was stirred under condition showed in table 1. The completion of the reaction was monitored by TLC using chloroform: methanol (8:2) as eluent and the obtained solid was filtered off and recrystalization from the ethanol solvent to give 3d-f.

2-propyl-3-p-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (3d)

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1676 (C=O), 1573(C=N) ; MS: m/z 205 [M^+]; ^{1}HNMR (DMSO) : δ 7.2 – 8.2 (m, 7H, aromatic), 2,9 (s, 3H, CH_3Ph), 2.5 (t, 2H, CH_2 CH_2Me), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3CH_2) ; Anal. calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36; N, 20.48; found: C, 58.51; H, 5.32; N, 20.44.

2-propyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (3d)

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1676 (C=O), 1573(C=N) ; MS: m/z 205 [M^+]; ^{1}HNMR (DMSO) : δ 7.2 – 8.2 (m, 7H, aromatic), 2,9 (s, 3H, CH_3Ph), 2.5 (t, 2H, CH_2 CH_2Me), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3CH_2) ; Anal. calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36; N, 20.48; found: C, 58.51; H, 5.32; N, 20.44.

2-propyl-3-m-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (3d)

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1676 (C=O), 1573(C=N) ; MS: m/z 205 [M^+]; ^{1}HNMR (DMSO) : δ 7.2 – 8.2 (m, 7H, aromatic), 2,9 (s, 3H, CH_3Ph), 2.5 (t, 2H, CH_2 CH_2Me), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3CH_2) ; Anal. calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36; N, 20.48; found: C, 58.51; H, 5.32; N, 20.44.

General procedure for preparation of 3 - (Arylylideneamino) - 2- propylpyrido [2,3-d] pyrimidin - 4(3H) - ones (4a-k)

Method (A). a mixture of aromatic aldehydes (10mmol) and compound 3-amino-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3a) (10 mmol) in 50 ml ethanol was reflux. The completion of the reaction was monitored by TLC using chloroform: methanol (8:2) as eluent and the obtained solid was filtered off and recrystalization from the ethanol solvent to give 4a-k.

Method (B). 3-amino-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (3a) (1 mmol, 0.204 g) and various substituted aromatic aldehydes (1 mmol) were added to ethanol (1 mL). The mixture was stirred for 5 min before the 0.1 mol/L aqueous solution of iodine/potassium iodide (10 mL) was added to this mixture. The mixture was stirred at room temperature except for compounds 4g which was refluxed for 15 min. The completion of the reaction was monitored by TLC using chloroform: methanol (8:2) as eluent. The resultant solid was filtered and washed with sodium thiosulphate solution 5% and hot water, respectively. The solid was pure enough but further purification can be achieved by recrystallization from ethanol.

Method (C). To a mixture of 3- amino – 2 –propylpyrido [2,3-d]pyrimidin-4(3H)-one (3a) added (1 mmol, 0.204 g) and various substituted aromatic aldehydes (1 mmol), an aqueous solution of iodine/potassium iodide (10 mL, 0.1 mol/L) was added. The mixture was refluxed for the indicated time (Table 2). The precipitant was filtered and washed with sodium thiosulphate solution 5% and hot water, respectively. The solid was pure enough but further purification can be achieved by recrystallization from ethanol.

3-(benzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4a).

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 292 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 8H, aromatic), 6.2(s,1H, N=CH), 2.7 (t,2H, CH_2pyrimidine), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{16}N_4O$: C, 69.86; H, 5.47; N, 19.17; found: C, 69.82; H, 5.44; N, 19.15.

3-(p-tolylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4b).

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2955, 2945, 2915, 2867 (CH aliphatic),1673 (C=O), 1598(C=N) ; MS: m/z 292 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.1(s,1H, N=CH), 2.35 (s, 3H, CH_3phenyl), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{18}H_{18}N_4O$: C, 70.12; H, 5.84; N, 18.18; found: C, 70.16; H, 5.81; N, 18.19.

3-(4-chlorobenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one(4c).

IR(KBr) cm^{-1} : 3030 (CH aromatic), 2975, 2939, 2911, 2876 (CH aliphatic),1671 (C=O), 1594(C=N) ; MS: m/z 326.5 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH), 2.7 (t, 2H, CH_2pyrimidine), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{15}N_4OCl$: C, 62.48; H, 4.59; N, 17.15; found: C, 69.82; H, 5.44; N, 19.15.

3-(4-nitrobenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4d).

IR(KBr) cm^{-1} : 3022 (CH aromatic), 2968, 2945, 2909, 2871 (CH aliphatic),1677 (C=O), 1599(C=N) ; MS: m/z 337 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH) 2.7 (t,2H, CH_2pyrimidine), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.45; N, 20.77; found: C, 60.52; H, 4.41; N, 20.74

3-(3-nitrobenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4e).

IR(KBr) cm^{-1} : 3022 (CH aromatic), 2968, 2945, 2909, 2871 (CH aliphatic),1677 (C=O), 1599(C=N) ; MS: m/z 337 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.2 (s,1H, N=CH) 2.7 (t,2H, CH_2pyrimidine), 1.9 (sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.45; N, 20.77; found: C, 60.52; H, 4.41; N, 20.74

3-(3-methoxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4f).

IR(KBr) cm^{-1} : 3022 (CH aromatic), 2979, 2945, 2915, 2870 (CH aliphatic),1673 (C=O), 1596(C=N) ; MS: m/z 322 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH), 3.75 (s, 3H ,O CH_3), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{18}H_{18}N_4O_2$: C, 67.08; H, 5.59; N, 17.39; found: C, 67.02; H, 5.54; N, 17.37.

3-(4-methoxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4g).

IR(KBr) cm^{-1} : 3022 (CH aromatic), 2979, 2945, 2915, 2870 (CH aliphatic),1673 (C=O), 1596(C=N) ; MS: m/z 322 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH), 3.75 (s, 3H ,O CH_3), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{18}H_{18}N_4O_2$: C, 67.08; H, 5.59; N, 17.39; found: C, 67.02; H, 5.54; N, 17.37.

3-(2-methoxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4h).

IR(KBr) cm^{-1} : 3022 (CH aromatic), 2979, 2945, 2915, 2870 (CH aliphatic),1673 (C=O), 1596(C=N) ; MS: m/z 322 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH) , 3.75 (s, 3H ,O CH_3), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{18}H_{18}N_4O_2$: C, 67.08; H, 5.59; N, 17.39; found: C, 67.10; H, 5.55; N, 17.36

3-(4-hydroxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4i).

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 310 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.4 (s,1H, N=CH), 5.25 (s, H ,OH), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{16}N_4O_2$: C, 65.80; H, 5.16; N, 18.06; found: C, 65.77; H, 5.12; N, 18.03.

3-(2-hydroxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one(4j).

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 310 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.3 (s,1H, N=CH), 5.25 (s, H ,OH), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{16}N_4O_2$: C, 65.80; H, 5.16; N, 18.06; found: C, 65.77; H, 5.12; N, 18.03.

3-(3-hydroxybenzylideneamino)-2-propylpyrido[2,3-d]pyrimidin-4(3H)-one (4k).

IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 310 [M^+]; ^{1}HNMR ($CHCl_3$) : δ 7.6 – 8.8 (m, 7H, aromatic), 6.5 (s,1H, N=CH) 5.25 (s, H ,OH), 2.7 (t,2H, CH_2pyrimidine), 1.9(sextet,2H,CH_2Me), 1.1(t, 3H, CH_3). Anal. calcd. for $C_{17}H_{16}N_4O_2$: C, 65.80; H, 5.16; N, 18.06; found: C, 65.77; H, 5.12; N, 18.03.

Acknowledgements

The authors are thankful to Basic & Health Science Research Center, Deanship of research Majmaah university for the financial support.

References

[1] S.N. VanderWel, P.J. Harvey, D.J. McNamara, J.T. Repine, P.R. Keller, J. Quin III, R.J. Booth, W.L. Elliott, E.M. Dobrusin, D.W. Fry, P.L. Toogood, J. Med. Chem 48 (2005) 2371e2378.

[2] P.L. Toogood, P.J. Harvey, J.T. Repine, D.J. Sheehan, S.N. VanderWel, H. Zhou, P.R. Keller, D.J. McNamara, D. Sherry, T. Zhu, J. Brodfuehrer, C. Choi, M.R. Barvian, D.W. Fry, J. Med. Chem 48 (2005) 2388e2406.

[3] B.D. Palmer, J.B. Smaill, G.W. Rewcastle, E.M. Dobrusin, A. Kraker, C.W. Moore, R.W. Steinkampf, W.A. Denny, Bioorg. Med.

[4] K. Malagu, H. Duggan, K. Menear, M. Hummersone, S. Gomez, C. Bailey, P. Edwards, J. Drzewiecki, F. Leroux, M.J. Quesada, G. Hermann, S. Maine, C. Molyneaux, A. Le Gall, J. Pullen, I. Hickson, L. Smith, S. Maguire, N. Martin, G. Smith, M. Pass, Bioorg. Med. Chem. Lett. 19 (2009) 5950e5953.

[5] X.L. Zhao, Y.F. Zhao, S.C. Guo, H.S. Song, D. Wang, P. Gong, Molecules 12 (2007) 1136e1146.

[6] H.N. Hafez, A.B.A. El-Gazzar, Bioorg. Med. Chem. Lett. 19 (2009) 4143e4147.

[7] A.S. Shawali, S.M. Sherif, M.A.A. Darwish, M.M. Elmerzabani, Arch. Pharm. Res. 33 (2010) 55e60.

[8] (a) Masuda, Satoru et al. Jpn.Kokai. Tokkyo Koho Jp 03, 106, 880. C.A.15: 183361d. (b) Tamura et al. Jpn. Kokai. Tokkyo Koho Jp 61, 249, 983, C.A. 106: 213979.

[9] J. Ram, D.A. Vanden Berghe, A.J.J. Vlietinck, Heterocycl. Chem. 28 (1988) 217.

[10] J.R. Piper, G.S. Mc Calab, J.A. Montgomery, R.L. Kishiuk, Y. Gamount, F.M. Sirotnak, J. Med. Chem. 29 (1986) 1080e1087.

[11] R.K. Robins, G.H.J. Hitchings, Am. Chem. Soc. 80 (1958) 3449.

[12] M.F. Hasan, A.M. Madkour, I. Saleem, J.M.A. Rahman, E.A.Z. Mohammed, Heterocycles 38 (1994) 57.

[13] John Adams Lowe,Chem. Abstr. 112 (1990) 21008 Austrian At. 388378 (1989) 378.

[14] A. Gangjee, O.O. Adair, S.F. Queener, J. Med. Chem. 46 (2003) 5074e5082. H. Iwamura, S. Murakami, K. Koshimizu, S. Matsabura, J. Med. Chem. 28 (1985)577e583.