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Synthesis and Spectroscopic Properties of Some Pyrimido[4,5-*b*]quinoline Derivatives

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Abstract. Several substituted pyrimido[4,5-b]quinoline were synthesized from the intermediates: 2-chloro-3-quinolinecarbonitrile (**1d**), 2-amino-3-quinolinecarbonitrile (**1h**) and 2-oxo-3-quinolinecarboxylic acid (**1g**), via cyclization with urea, thiourea, guanidine, formamide and acetic anhydride. Structural elucidation of the prepared quinolines and pyrimido[4,5-b]quinolines was mainly based on the spectroscopic methods, and in particular, MS and NMR spectra.

Introduction

Numerous quinolines, pyrimidines and pyrimido-quinoline derivatives have been prepared and their pharmacological properties were evaluated. Many of these compounds have proved to be active anticancers [1, 2], anti-inflammatories [3], antiallergics [4] and antimicrobials [5-8]. Further, the utility of quinoline derivatives in the preparation of some dyes and pigments has been reported [9]. All this prompted our interest to continue the work directed to the synthesis of some novel pyrimido[4,5-*b*]quinoline derivatives of the expected biological activity, starting with quinoline derivatives.

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Experimental

Melting points were determined on a Tottoli capillary melting point apparatus and are uncorrected. IR spectra were run for KBr discs on Perkin Elmer FT spectrophotometer 1000. ^{1}H and ^{13}C NMR spectra were taken on JEOL NMR spectrometer ECP 400 in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Chemical shift is given in δ ppm and coupling constants (*J)* are given in Hz. Electron impact (EI) MS spectra were carried on Shimadzu GCMSQP5050A spectrometer, DB-1 glass column 30 m, 0.25 mm, ionization energy 70 eV, at Chemistry Department, College of Science, King Saud University. Electrospray ionization (ESI) MS spectra were carried on Quattro LC triple quadruple mass spectrometer at research center King Faisal Specialist Hospital. Microanalyses were carried out at the central laboratory of King Saud University, Women Students, Medical Studies and Science Sections.

Preparation of 2-chloro-3-formylquinoline (1)

This compound was prepared as reported [10]. It was characterized by ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2).

Preparation of 3-formyl-2-quinolone (1a)

It was prepared as reported [11]. Yield 93%, m.p. 290-291°C (as reported). IR (cm^{-1}): 3446 (NH), 3006 (CH aryl), 2867, 2781, (CH aldehyde), 1686 (C=O aldehyde) and 1668 (C=O lactam).

Preparation of 3-hydroxyiminomethyl-2-quinolone (1b)

It was prepared as reported [11]. Yield 84%, m.p. 246-247°C (as reported). IR (cm^{-1}): 3304-3132 (OH), 3233 (NH) and 1660 (C=O lactam).

Preparation of 1,2-dihydro-2-oxo-3-quinolinecarbonitrile (1c)

It was prepared as reported [11]. Yield 90%, m.p. 301-302°C (as reported). IR (cm^{-1}): 3446 (NH), 2231 (C≡N) and 1665 (C=O lactam).

Preparation of 2-chloro-3-quinolinecarbonitrile (1d)

It was prepared by two methods as reported [11, 12]. Yield 79%, (first method) 97% (second method) m.p. 158-159°C (as reported). ^{1}H NMR (Table 1), ^{13}C NMR (Table 2), IR and MS (Table 3).

Preparation of 2-chloro-3-hydroxyiminomethylquinoline (1e)

It was prepared as reported [11]. Yield 92%, m.p. above 300°C (as reported). ^{1}H NMR (Table 1), ^{13}C NMR (Table 2), IR and MS (Table 3).

Preparation of 1,2-dihydro-2-thioxo-3-quinolinecarbonitrile (1f)

Thiourea (0.76 g, 0.01 mol) was added to a solution of (**1d**) (1.88 g, 0.01 mol) in DMF (30 ml) with stirring. The reaction mixture was refluxed for 2 h, a yellow precipitate was formed, filtered, washed with water and recrystallized form ethanol,

yield 66%, m.p. 284-285°C. ^{1}H NMR (Table 1), IR and MS (Table 3). Compound (**1f**) was also obtained when replacing DMF by water.

Preparation of 1,2-dihydro-2-oxo-3-quinolinecarboxylic acid (1g)

A mixture of (**1c**) (1.70 g, 0.01 mol) and 70% H_2SO_4 (22 ml) was refluxed for 5 h, then cooled, poured onto ice cold water (100 ml). The formed precipitate was filtered, washed with water, dried and purified on TLC silica gel plates using benzene-ethyl acetate (1:1), yield 84%, m.p. above 300°C. ^{1}H NMR (Table 1), IR and MS (Table 3).

Preparation of synthesis of 2-amino- 3-quinolinecarbonitrile (1h)

It was prepared as reported [13].Yield 76% m.p. 228-230°C (as reported). ^{1}H NMR (Table 1) ^{13}C NMR (Table 2), IR and MS (Table 3).

Preparation of 4-amino-2-substituted pyrimido[4,5-b]quinolines (2a, b)

General method:

A mixture of (**1d**) (1.88 g, 0.01 mol) and thiourea (3.8 g, 0.05 mol) or urea (3.0 g, 0.05 mol) was fused at 260-300 °C using sand bath for 1 h with continuous stirring, then cooled to room temperature. The crude solid product was washed with water, then with 5% $NaHCO_3$ and finally with ethanol, recrystallized from DMF/H_2O to afford (**2a**) and (**2b**), respectively. Compound (**1h**) was treated in the same way and gives the same products (**2a**) and **(2b**):

Compound (**2a**): Yield 85%, m.p. >300°C. IR and MS (Table 3), ^{1}H NMR (Table 4), ^{13}C NMR (Table 5).

Compound (**2b**): Yield 63%, m.p. >300°C. IR and MS: (Table 3), ^{1}H NMR (Table 4), ^{13}C NMR (Table 5).

Preparation of 2,4-diaminopyrimido[4,5-b]quinoline (2c)

Sodium metal (0.23 g, 0.01 mol) was dissolved in 1-butanol (100 ml), and then guanidine hydrochloride (0.94 g, 0.01 mol) and compound (**1h**) (0.85 g, 0.005 mol) were added with stirring. The reaction mixture was refluxed for 6 h. A yellow solid was formed, filtered, washed with 1-butanol, dried and recrystallized from water, yield 74%., m.p. >300°C, IR and MS (Table 3), ^{1}H NMR (Table 4).

Preparation of 2-arylamino-3-quinolinecarbonitrile (3a-c)

Method A:

A mixture of (**1d**) (1.88 g, 0.01 mol) and the appropriate aromatic primary amine (0.05 mol) was fused on an oil bath at 110-140°C for 6-42 h with continuous stirring, and then left for 4 h at room temperature. The crude solid was triturated with cold water, filtered, dried and recrystallized from ethanol. Compound (**3c**) was purified by TLC silica gel plates using benzene-ethyl acetate (1:1) as an eluant.

Method B:

A mixture of (**1d**) (1.88 g, 0.01 mol), DMF (15 ml) and the appropriate amine (0.01 mol) was refluxed for 18-24 h, then cooled and treated with 5% K_2CO_3 solution. The crude solid obtained was filtered, washed with water and recrystallized from ethanol.

Compound (**3a**): Yield 65%, m.p. 178°C, IR and MS (Table 3), ^{1}H NMR (Table 4), ^{13}C NMR (Table 5).

Compound (**3b**): Yield 55%, m.p. 191°C, IR and MS (Table 3), ^{1}H NMR (Table 4).

Compound (**3c**): Yield 75%, m.p. 121°C, IR and MS (Table 3), ^{1}H NMR (Table 4), ^{13}C NMR (Table 5).

Preparation of 4-amino-1-aryl-2-thioxopyrimido[4,5-b]quinoline (4a-c)

A mixture of the relevant arylaminoquinoline (**3**) (0.01 mol) and thiourea (0.05 mol) was fused at 260-300 °C using sand bath for 1-2 h, then cooled to room temperature, the crude solid was triturated with water, filtered, dried and recrystallized from the appropriate solvent.

Compound (**4a**): Crystallized from DMF/H_2O, yield 70%, m.p. >300 °C, IR and MS (Table 3).

Compound (**4b**): Crystallized from DMF/H_2O, yield 65%, m.p. >300°C, IR and MS (Table 3).

Compound (**4c**): Crystallized from DMF/EtOH, yield 80%, m.p. 204-206 °C, IR and MS (Table 3).

Preparation of 2-hydroxy-3-ureidocarbonylquinoline (6)

A mixture of (**1g**) (0.56 g, 0.003 mol) and thionyl chloride (25 ml) was refluxed for 1.5 h, and then distilled under reduced pressure. The residue was treated with benzene and redistilled. This process was repeated three times in order to remove the extra thionyl chloride. The prepared acyl derivative (**5**) was then treated with urea (0.16 g, 0.003 mol) and toluene (5 ml). The mixture was refluxed for 3 h and cooled. The solid product was filtered, triturated with 5% Na_2CO_3 solution, filtered and recrystallized from DMF/EtOH (1:1), yield 48%, m.p. 248-249 °C. IR and MS (Table 3), ^{1}H NMR (Table 4).

Preparation of 2-hydroxy-3-thioureidocarbonylquinoline (7)

It was prepared by the same procedure used for preparation of (**6**), recrystallized from DMF/ethanol (1:1), yield 62%, m.p. >300 °C. IR and MS (Table 3).

Preparation of 2-Thioxopyrimido[4,5-b]quinolin-4-(3H)-one (8)

The thioureido derivative (**7**) (2.47 g, 0.01 mol) was refluxed in dry xylene (5 ml) for 5 h. The solid which produced after cooling was filtered off, dried and recrystallized from DMF/H_2O yield 50%, m.p. > 300° C. IR and MS (Table 3), ^{1}H NMR (Table 4).

Preparation of 2-amino-3-quinolinecarboxylic acid (9)

The thioureido derivative (**7**) (1.5 g, 0.008 mol) was fused at 260-300 °C for 1 h with stirring. After cooling to room temperature, the solid product was purified by sublimation yield 87.5%, m.p. >300°C, (Ref. [13] m.p. 320-320.5°C). IR and MS (Table 3), ^{1}H NMR (Table 4).

Preparation of 4-aminopyrimido[4,5-b]quinoline (10)

It was prepared according to Ref. [14]. m.p.>300°C, (Ref. [14] m.p.>325°C). IR and MS (Table 3), ^{1}H NMR (Table 4).

Preparation of 2-acetylamino-3-quinolinecarbonitrile (11)

A mixture of (**1h**) (1.69 g, 0.01 mol) and acetic anhydride (3 ml) was refluxed for 24 h, and then cooled, poured onto ice-cold water, left for 2 h and filtered. A white crystalline solid product was obtained, filtered, dried and recrystallized from ethanol, yield 35%, m.p. 116-118 °C. IR and MS (Table 3), ^{1}H NMR (Table 4), ^{13}C NMR (Table 5).

Preparation of 2-Methylpyrimido[4,5-b]quinoline-4-(3H)-one (12)

Method A:

A mixture of (**11**) (2.11 g, 0.001 mol), acetic anhydride (3 ml) and conc. H_2SO_4 (0.5 ml) was heated in a boiling water bath for 10 min., then cooled, poured onto ice-cold water, treated with 20% NaOH solution till alkaline (pH 11), the crude solid product was filtered and recrystallized from water, yield 40%, m.p. above 300 °C.

Method B:

A mixture of (**1h**) (1.69 g, 0.01 mol), acetic anhydride (3 ml) and conc. H_2SO_4 (0.5 ml) was refluxed for 9 h, then treated as in method A, yield 70% m.p. above 300 °C. IR and MS (Table 3), ^{1}H NMR (Table 4).

Results and Discussion

The starting material 2-chloro-3-formylquinoline (**1**) was prepared following a well-established method via the reaction of acetanilide with Vilsmeir reagent [10]. It was converted to the corresponding oxime (**1e**) according to Lit. method [11,12]. ^{1}H NMR of this oxime exhibits a singlet (1H) at δ 8.75 for (C<u>H</u>=NOH), a singlet (1H) at δ 11.98 for (CH=NO<u>H</u>), beside the aromatic protons of the quinoline nucleus (Table 1). The ^{13}C NMR data are shown in Table 2. The structure of the oxime (**1e**) was further confirmed by its mass spectrum that showed a molecular ion peak [M^+] ($C_{10}H_7{}^{35}ClN_2O$) at m/z = 206 (100%) and [M+2] peak at *m/z* = 208 ($C_{10}H_7{}^{37}ClN_2O$) (33%). The oxime (**1e**) was dehydrated by acetic anhydride to afford the corresponding nitrile (**1d**). The IR spectrum

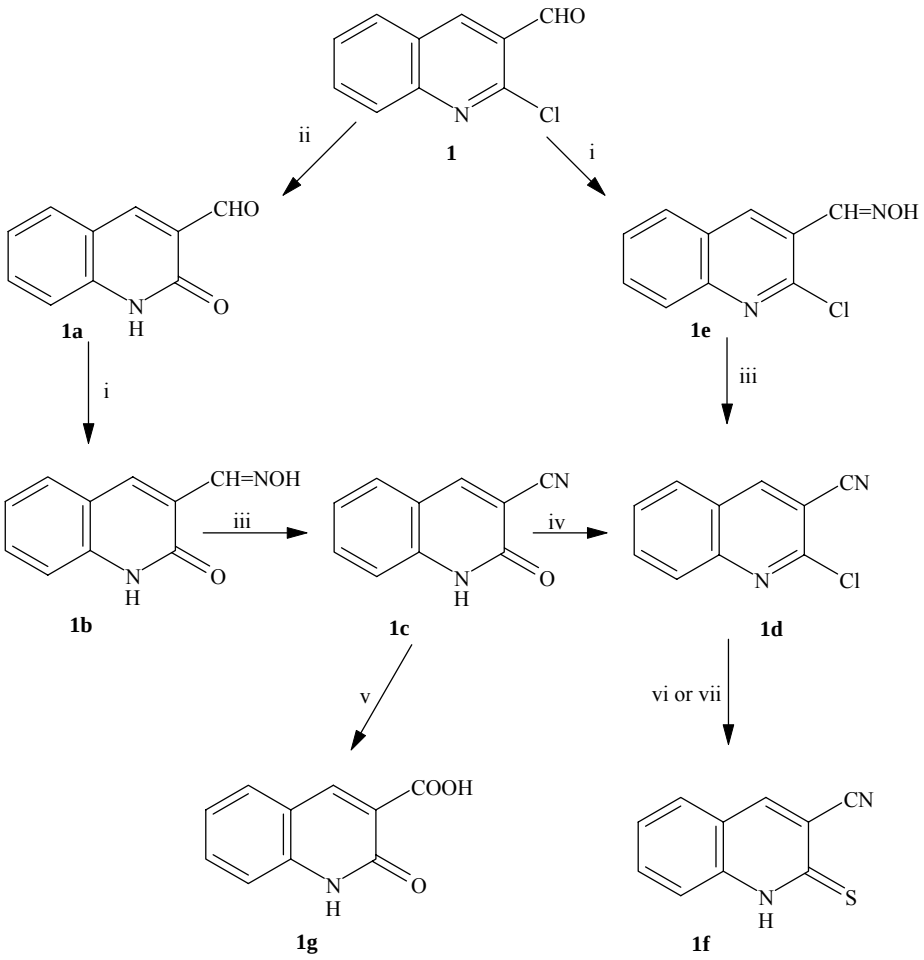
of (**1d**) showed a sharp band at 2232 cm^{-1} characteristic of the cyano group. The ^{1}H and ^{13}C NMR spectral data are recorded in Tables 1 and 2 respectively. The mass spectrum of (**1d**) showed a molecular ion peak at *m/z* = 188 [M^{+}] (13%) ($C_{10}H_5{}^{35}ClN_2$) and [M+2] at m/z = 190 (4%) ($C_{10}H_5{}^{37}ClN_2$). The nitrile (**1d**) was prepared by another route [11], in which the chloroquinoline derivative (**1**) was subjected to nucleophilic substitution by the hydroxyl group using 50% HCl to give the lactam (**1a**), which in turn converted to the corresponding oxime (**1b**). The latter was dehydrated by acetic anhydride to give the nitrile (**1c**). The reaction of $POCl_3$ with (**1c**) yielded (**1d**) but in a lower yield than the previous route (Scheme 1). A trial to cyclize (**1d**) with thiourea in DMF in order to obtain the pyrimidoquinoline derivative was failed, instead we obtained 3-cyano-2-thioxoquinoline (**1f**), i.e. nucleophilic substitution of the chloride anion by the mercapto group occurred rather than cyclization. The reaction was repeated in water and we obtained the same result [15]. The nitrile (**1c**) was hydrolyzed by 70% H_2SO_4 to give the corresponding acid (**1g**) which was used later for further cyclization. The ^{1}H NMR spectral data of (**1**, **1d**, **1e**, **1f, 1g** and **1h**) are in Table 1. The ^{13}C NMR spectral data of (**1**, **1d**, **1e**, and **1h**) are in Table 2.

Table 1. ^{1}H NMR spectral data of quinoline derivatives (1, 1d, 1e, 1g and 1h) in DMSO-d_6 or $CDCl_3$*

	1*	**1d**	**1e**	**1f**	**1g**	**1h**
C_4-H	8.76, s	9.27, s	8.41, s	8.76, s	8.51, s	8.66, s
C_5-H	7.98, d, (8)	8.05, m	7.94, d, (8.0)	7.63, d, (8.4)	7.36, d, (8.0)	7.51, d, (8.8)
C_6-H	7.65, t, (7.3)	7.82 t, (8.3)	7.66, t, (8.0)	7.44, t, (7.3)	7.26, t, (7.3)	7.26, t, (8.3)
C_7-H	7.88, t, (7.3)	8.0, m	7.83, t, (7.3)	7.80, t, (7.7)	7.66, t, (8.0)	7.65, td, (8.0, 1.3)
C_8-H	8.07, d, (8.0)	8.15 d, (8.3)	8.12, d, (8.0)	7.86, d, (7.7)	7.92, d, (8.0)	7.74, d, (8.1)
CHO	10.55, s	-	-	-	-	-
COOH	-	-	-	-	12.22, s	-
NH_2	-	-	-	-	-	6.94, br.s **
NH	-	-	-	14.21	10.24, br.s **	-
CH=NOH	-	-	8.75, s, 11.98, br.s**	-	-	-

**D_2O exchangeable. (*J* values in Hz)

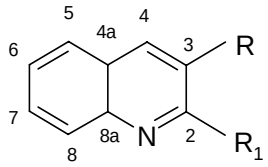
2-chloro-3-quinolinecarbonitrile (**1d**) was fused with thiourea and urea at 260-300°C to yield (**2a**) and (**2b**) respectively. These last two compounds were also prepared from the starting material 2-amino-3-quinolinecarbonitrile (**1h**) by fusion with thiourea and urea [14, 16]. Unsuccessful results were obtained on repeating the same procedure using guanidine salt instead of urea and thiourea, this may be attributed to the low nucleophilicity of guanidinium ion in the salt form. Handling of free guanidine is difficult as it rapidly absorbs carbon dioxide and moisture from air forming the stable guanidinium hydrogen carbonate. Furthermore, free guanidine is thermally unstable and, when heated at elevated temperature in the presence of alkali, it readily undergoes decomposition to carbon dioxide, and urea [17]. IR spectra determined the structures of (**2a**) and (**2b**), which indicated the disappearance of the cyano group, and the appearance of (C=S) at 1239cm^{-1} for (**2a)** and (C=O) at 1619cm^{-1} for (**2b**) (Table 3).



i = H_2NOH, ii = 50% HCl, iii = Ac_2O, iv = $POCl_3$
v = 70% H_2SO_4, vi = thiourea / DMF, vii = thiourea / H_2O.

Scheme 1

Table 2. ^{13}C spectral data of (1, 1d, 1e and 1h) in DMSO-d_6 or $CDCl_3$[*]

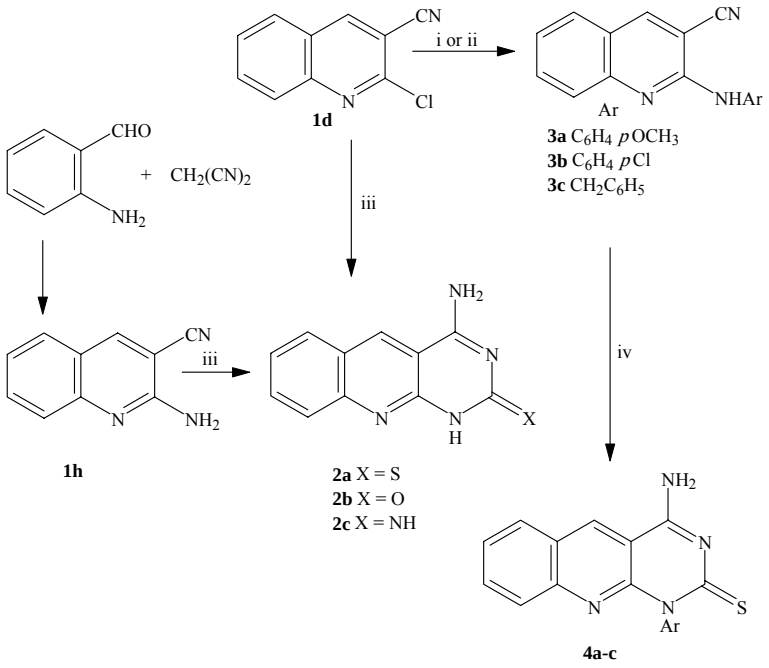


C-Assignment	1[*]	1d	1e	1h
R, R_1	CHO, Cl	CN, Cl	CHNOH, Cl	CN, NH_2
C_2	150.02	148.55	148.52	156.25
C_3	126.62	107.41	127.33	95.11
C_4	140.40	144.66	136.14	145.93
C_{4a}	126.44	128.35	125.44	117.06
C_5	128.69	129.27	128.31	125.97
C_6	128.24	128.63	128.15	123.40
C_7	129.81	129.44	129.22	129.09
C_8	133.71	134.96	132.07	133.48
C_{8a}	149.67	148.04	147.46	149.55
CHO	189.27	-	-	-
CN	-	116.04	-	121.50
CHNOH	-	-	144.64	-

2,4-diaminopyrimido[4,5-*b*]quinoline (**2c**) was obtained in 74% yield by heating (**1h**) with guanidine HCl in sod. butoxide / butanol mixture [18] (Scheme 2). The IR spectrum of (**2c**) disclosed the disappearance of the cyano group, while the ^1H NMR spectrum showed two broad singlet at δ 7.80 and 8.25 for the two NH_2 groups, as well as the signals of the aromatic protons (Table 4). The structure of (**2c**) was further confirmed by its mass spectrum. The mass spectra of compounds (**2a-c**) are characterized by common fragments at *m/z*: 170 [M-NCS] (100%) for (**2a**), 169 [M-HNCO] (58%) for (**2b**), and 169[M-$NCNH_2$] (20%) for (**2c**). These fragments are due to Retro Diels-Alder fragmentation [19] (RDA) (Table 3).

It has been reported that some pyrimidoquinoline derivatives have strong tendency to retain water of crystallization and high temperatures under reduced pressure are needed to get the correct elemental analyses [20].

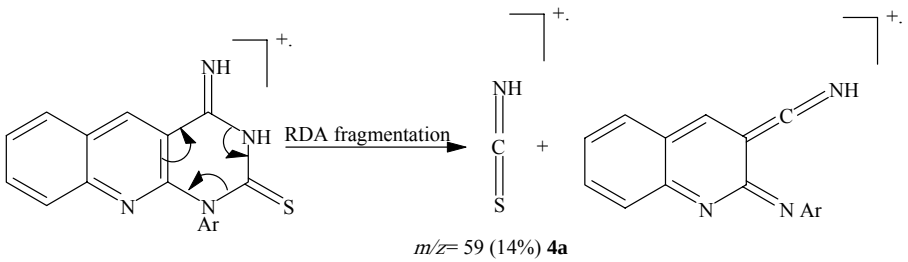
2-chloro-3-quinolinecarbonitrile (**1d**) was subjected to aromatic nucleophilic substitution by primary amines. This was done by two methods, either by fusing (**1d**) with the corresponding amine at 110-140°C [21] or by heating (**1d**) with the amine under reflux in DMF. Both methods gave, more or less, the same yield of 2-arylaminoquinoline-3-carbonitrile (**3a-c**), but the products obtained from the second method were more pure and easily isolated.



i = fusion with $ArNH_2$ at 110-140ºC, ii = reflux with $ArNH_2$ in DMF

iii = thiourea, urea or guanidine, iv = thiourea.

Scheme 2



4a C_6H_4 *p*OCH_3
4b C_6H_4 *p*Cl
4c $CH_2C_6H_5$

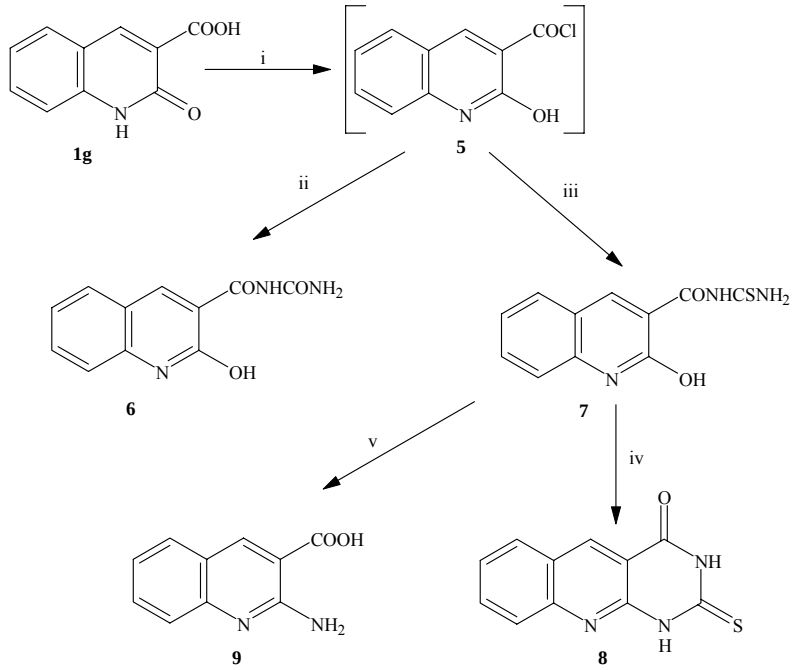
m/z= 59 (14%) **4a**
58 (4%, M-1) **4b**
59 (7%) **4c**

m/z= 275 (3%, $C_{17}H_{13}N_3O$) **4a**
279 (10%, $C_{16}H_{10}{}^{35}ClN_3$) **4b**
281(4%, $C_{16}H_{10}{}^{37}ClN_3$) **4b**
259 (100%, $C_{17}H_{13}N_3$) **4c**

Scheme 3

Compounds (**3a-c**) were fused with thiourea to afford 4-amino-1-aryl-2-thioxopyrimido [4,5-*b*]quinoline (**4a-c**) [22] (Scheme 2). IR spectra showed the disappearance of the cyano group stretching absorption, and the appearance of NH_2 stretching in the range 3484-3164cm^{-1} and C=S stretching at 1165-1154 cm^{-1}. The mass spectra of these compounds are characterized by the presence of two fragments due to RDA fragmentation, one at *m/z* = 59 for $[HNCS]^{+\cdot}$ and the other for $[M\text{-}HNCS]^{+\cdot}$ (Scheme 3).

1,2-dihydro-2-oxo-3-quinolinecarboxlyic acid (**1g**) was converted to the acid chloride (**5**) by $SOCl_2$. Compound (**5**) was treated directly without isolation with urea and thiourea to give the ureido and the thioureido derivatives (**6**) and (**7**) respectively [23] (Scheme 4). Their structures were confirmed by IR, ^{1}H NMR and MS spectral data (Tables 3 and 4). Compound (**7**) was cyclized by heating under reflux in xylene to afford the 2-thioxopyrimido[4,5-*b*]quinolin-4-(3H)-one (**8**). The ^{1}H NMR spectrum of (**8**) exhibited two broad singlets at δ 12.59 and 12.85 ppm assigned for the two NH groups beside the signals of the aromatic protons of the quinoline nucleus. The mass spectrum showed a peak at *m/z* = 228 [M-1] (6%) and other two fragments from RDA fragmentation, one at *m/z* = 59 (100%) for $[HNCS]^{+\cdot}$ and the other at *m/z* = 170 (3%) for $[M\text{-}HCNS]^{+}$.



i = $SOCl_2$, ii = urea / toluene reflux, iii = thiourea / toluene reflux
iv = reflux in xylene, v = fusion.

Scheme 4

Table 3. (EI) (ESI*) MS spectral data of compounds (1d-1h, 2-4 and 6-12)

Compd. No.	*m/e* (%)	IR (cm^{-1})
1d	188 [M^+] (13) ($C_{10}H_5{}^{35}ClN_2$), 190[M+2] (4) ($C_{10}H_5{}^{37}ClN_2$).	2230 (C≡N).
1e	206 [M^+] (100) ($C_{10}H_7{}^{35}ClN_2O$), 208 [M+2] (33) ($C_{10}H_7{}^{37}ClN_2O$), 171 [M-Cl] (12).	3546-3304 (OH), 1637 (C=N).
1f	186 [M^+] (100) ($C_{10}H_6N_2S$), 159 [M-HCN] (21), 153 [M-SH] (38).	3416 (NH), 2231 (C≡N), 1229 (C=S).
1g	189 [M^+] (9) ($C_{10}H_7NO_3$), 145 [M–COOH +H] (100).	3415 (NH), 3200-2400 (OH), 1743 (C=O carboxylic), 1672 (C=O lactam).
1h	169 [M^+] (100) ($C_{10}H_7N_3$).	3395, 3328 (NH_2), 2226 (C≡N).
2a	229 [M+1] (25) ($C_{11}H_8N_4S$), 212 [M-NH_2] (23), 170 [M-NCS] (100).	3395, 3328 (NH_2), 2226 (C≡N). 1239 (C=S)
2b	212 [M^+] (100) ($C_{11}H_8N_4O$), 196 [M-NH_2] (8), 170 [M-NCO] (62), 169 [M-HNCO] (58).	3375, 3164 (NH_2), 1619 (C=O).
2c	211 [M^+] (100) ($C_{11}H_9N_5$), 195 [M-NH_2] (15), 169 [M-$NCNH_2$] (20).	3401, 3320 (NH_2).
3a	275 [M^+] (72), ($C_{17}H_{13}N_3O$).	3329 (NH), 2226 (CN).
3b	279 [M^+] (67), ($C_{16}H_{10}ClN_3$), 281 [M+2] (23)	3343 (NH), 2227 (CN).
3c	259 [M^+] ($C_{17}H_{13}N_3$), (93).	3381 (NH), 2217 (CN).
4a*	334 [M^+] (5). ($C_{18}H_{14}N_4OS$.), 319 [M-CH_3] (20), 318 [M-NH_2] (100), 304 [M-OCH_2] (43%), 275 [M-HNCS] (3), 59 [HNCS]$^+$ (14).	3484, 3330(NH_2), 1154 (C=S)
4b*	279 [M-HNCS] (10) ($C_{16}H_{10}{}^{35}ClN_3$), 281 [M+2-HNCS] (4) ($C_{16}H_{10}{}^{37}ClN_3$), 243 [M-HNCS-HCl] (3).	3390, 3254 (NH_2), 1160 (C=S)
4c*	317 [M-1] (2) ($C_{18}H_{13}N_4S$), 260 [M-NCS] (7), 259 [M-HNCS] (100), 227 [M-CH_2ph] (13), 91 [tropylium ion] (2), 59 [HNCS]$^+$ (7).	3413, 3164 (NH_2), 1165 (C=S)
6*	231 [M^+] (22) ($C_{11}H_9N_3O_3$), 214 [M-NH_3] (20), 188 [M-$CONH_2$+H] (99).	3382 (NH), 3140-3182 (OH), 3179, 3138 (NH_2), 1698, 1642 (2C=O).
7*	247 [M^+] (14) ($C_{11}H_9N_3O_2S$), 229 [M-H_2O] (5).	1656 (C=O), 1153 (C=S).
8*	228 [M-1] (6) ($C_{11}H_6N_3OS$), 170 [M-HNCS] (3), 59 [$HNCS^+$] (100).	3420, 3460 (2NH), 1633 (C=O), 1161 (C=S).
9	188 [M^+] (87) ($C_{10}H_8N_2O_2$), 170 [M-H_2O] (17), 144 [M-CO_2] (100), 143 [M-COOH] (78).	3664-2804 (OH), 3476, 4313 (NH_2), 1679 (C=O).
10*	197 [M+1] (100) ($C_{11}H_8N_4$), 170 [M-HCN+H] (16).	3475, 3410 (NH_2).
11*	212 [M+1] (13).	3475, 3410 (NH_2).
12*	212 [M+1] (100), 183 [M-CO] (3).	3431 (NH), 1707 (C=O).

Table 4. ^{1}H NMR spectral data (δ in ppm, J in Hz) in DMSO-d_6 (*$CDCl_3$)

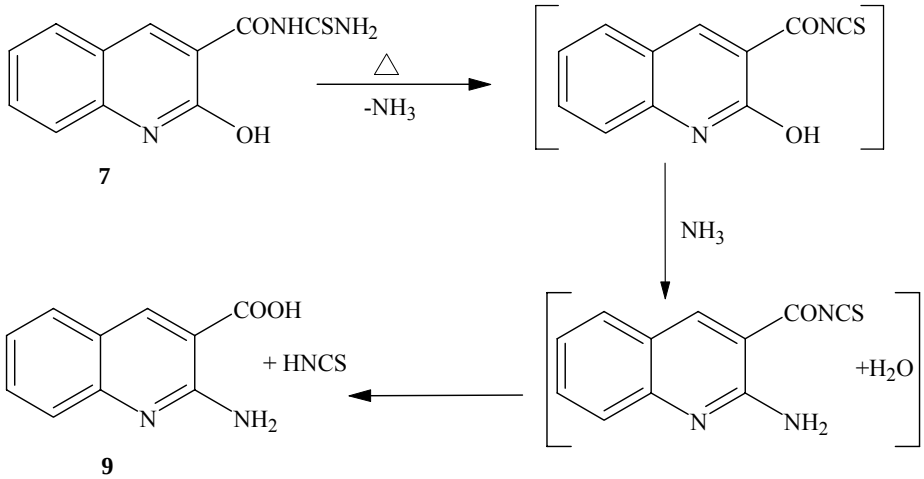
Compd. No.	^{1}H NMR
2a*	7.33 (4H, m, C_6-H, C_7-H, NH_2), 7.43 (2H, m, C_8-H, C_9-H), 8.25 (1H, s, C_5-H), 12.09 (1H, br.s, NH)**.
2b	7.51 (1H, t, *J* = 7.0 , C_8-H), 7.81 (2H, m, C_6-H, C_7-H), 7.91 (1H, d, *J* = 8.0 , C_9-H), 8.31 (2H, br.s, NH_2)**, 9.11 (1H, s, C_5-H), 11.11 (1H, br.s, NH)**.
2c	7.13 (2H, br.s, D_2O exchangeable, NH_2), 7.45 (1H, t, *J* = 8.0, C_8-H), 7.80 (2H, m, C_6-H, C_7-H), 7.89 (1H, d, *J* = 8.0 , C_9-H), 8.25 (2H, br.s, NH_2)**.
3a	3.77 (3H, s, OCH_3), 6.93 (2H, d, *J* = 8.8 , phenyl H), 7.37 (1H, t, *J* = 7.3, C_6-H), 7.56 (1H, d, *J* = 7.3 , C_5-H), 7.66 (2H, d, *J* = 8.8 , phenyl H), 7.70 (1H, t, *J* = 8.0 , C_7-H), 7.81 (1H, d, *J* = 8.1 , C_8-H), 8.82 (1H, s, C_4-H), 8.93 (1H, br.s, NH)**.
3b	7.39 (2H, d, *J* = 8.6 ,phenyl H), 7.43 (1H, t, *J* = 8.6 , C_6-H), 7.66 (1H, d, *J* = 8.6 , C_5-H), 7.70 (1H, t, *J* = 8.6 , C_7-H), 7.85-7.88 (3H, m, C_8-H + 2 phenyl H's), 8.91 (1H, s, C_4-H), 9.25 (1H, br.s, NH)**.
3c	4.68 (2H, d, *J* = 5.9 , CH_2), 7.20 (1H, t, *J* = 7.3 , phenyl H), 7.26-7.32 (3H, m, C_6-H + phenyl H), 7.41 (2H, d, *J* = 7.3 , phenyl H), 7.52 (1H, d, *J* = 8.8 , C_5-H), 7.64 (1H, t, *J* = 8.0 , C_7-H), 7.74 (1H, d, *J* = 8.0 , C_8-H), 8.70 (1H, s, C_4-H), 7.83 (1H, t, *J* = 5.9 , NH)**.
6	7.32 (1H, t, *J* = 7.7 , C_6-H), 7.43 (1H, d, *J* = 8 , C_5-H), 7.49 (2H, br.s, NH_2)**, 7.71 (1H, t, *J* = 8.4 , C_7-H), 7.88 (1H, s, OH), 8.0 (1H, d, *J* = 7.7 , C_8-H), 8.98 (1H, s, C_4-H), 11.77 (1H, br.s, NH)**.
8	7.34 (1H, t, *J* = 7.3 , C_7-H), 7.46 (1H, d, *J* = 8.5 , C_6-H), 7.73 (1H, t, *J* = 8.5 , C_8-H), 8.01 (1H, d, *J* = 8.5 , C_9-H), 9.0 (1H, s, C_5-H), 12.59 (1H, br.s, NH)**, 12.85 (1H, br. s, NH)**.
9	4.5 (2H, br.s, NH_2)**, 7.31 (1H, t, *J* = 7.3 , C_6-H), 7.38 (1H, d, *J* = 8.3 , C_5-H), 7.71 (1H, t, *J* = 8.1 , C_7-H), 7.79 (1H, d, *J* = 7.7 , C_8-H), 8.81 (1H, s, C_4-H), 12.5 (1H, s, COOH)**.
10	6.25 (2H, br.s, NH_2)**, 6.82 (2H, m, C_6-H, C_7-H), 7.00 (2H, m, C_8-H, C_9-H), 7.84 (1H, s, C_5-H), 9.07 (1H, s, C_2-H).
11	2.30 (3H, s, CH_3), 7.87 (1H, t, *J* = 8.0 , C_6-H), 8.05 (1H, t, *J* = 8.0 , C_7-H), 8.12 (1H, d, *J* = 8.0 , C_5-H), 8.20 (1H, d, *J* = 8.0 , C_8-H), 9.25 (1H, s, C_4-H), 11.05 (1H, br.s, NH)**.
12	2.26 (3H, s, CH_3), 7.37 (1H, t, *J* = 7.0 , C_7-H), 7.67 (1H, t, *J* = 7.0 , C_8-H), 7.82 (1H, d, *J* = 8.0 , C_6-H), 8.01 (1H, d, *J* = 8.0 , C_9-H), 8.86 (1H, s, C_5-H)

** D_2O exchangeable

Table 5. ^{13}C NMR Spectral data (δ in ppm) in DMSO-d_6 (*$CDCl_3$)

Compd No.	C-Ar	Other C
2a*	113.01, 125.54, 125.86, 127.57, 129.95, 130.50, 130.90, 136.25, 149.98, 166.47.	176.25 (C=S).
2b	106.35, 124.60, 125.26, 127.18, 129.95, 133.37, 135.94, 149.92, 151.63, 158.40 .	163.78 (C=O).
3a	96.70, 113.98, 122.01, 123.72, 124.23, 126.65, 128.79, 133.02, 133.52, 146.36, 148.33, 152.32, 155.68.	55.53 (OCH_3), 116.63 (C≡N).
3c	95.83, 121.52, 123.45, 126.62, 127.14, 128.10, 128.70, 129.08, 133.46, 140.55, 145.97, 149.25, 154.31.	44.48 (CH_2), 116.95 (C≡N).
11	106.80, 129.40, 130.12, 133.12, 134.62, 144.58, 146.82, 147.73, 157.74.	26.49 (CH_3), 119.12 (C≡N), 172.59 (C=O).

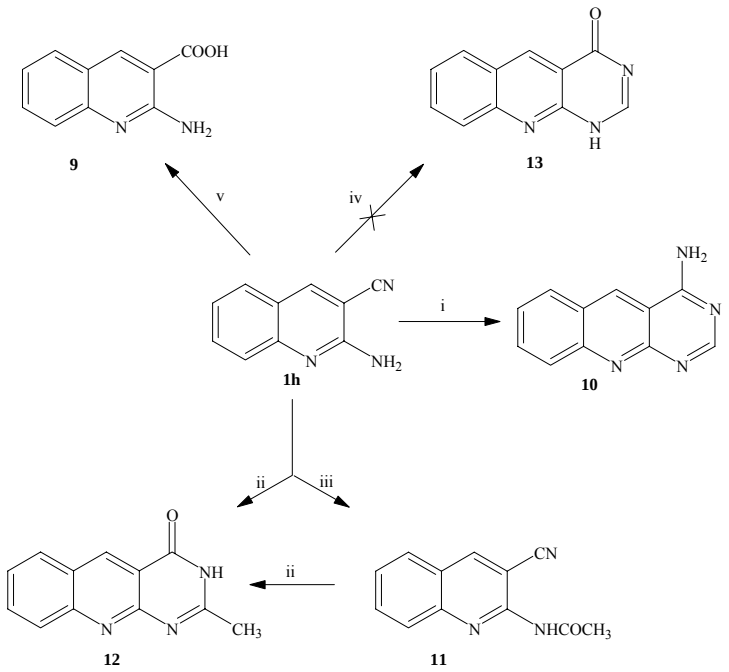
An attempt to cyclize (**7**) by fusion at 260-300°C yielded 2-amino-3-quinolinecarboxylic acid (**9**) instead of (**8**). The structure of (**9**) was determined by its spectral data. Hence, its IR spectrum showed OH stretching band of the carboxylic group at 3664-2804 cm^{-1} and C=O stretching band at 1679cm^{-1}. The ^{1}H NMR spectrum of this compound disclosed a singlet at δ 12.5 ppm for COOH and a broad singlet at δ 4.5 ppm for NH_2 in addition to the other bands of the aromatic protons. The mass spectrum showed a molecular ion peak at m/z = 188 (87%) for $C_{10}H_8N_2O_2$ beside other fragments at m/z: 170 [M-H_2O] (17%), 144 [M-CO_2] (100%) and at 143 [M-$COOH^{\cdot}$] (78%). A comparison between the mass spectrum of (**9**) and that of an authentic sample of 2-aminonicotinic acid has been made and which revealed that both are identical. Accordingly, we suggest the formation of (**9**) as shown in Scheme 5.



Scheme 5

Treatment of (**1h**) with formamide afforded 4-aminopyrimido[4,5-*b*]quinoline (**10**). Acetylation of (**1h**) gave the N-acetyl derivative (**11**), which was cyclized using a mixture of Ac_2O / H_2SO_4 to give 2-methylpyrimido[4,5-*b*]quinolin-4-(3H)-one (**12**) in 40% yield. On the other hand, the latter compound was obtained in 70% yield directly form (**1h**) when it was treated with a mixture of Ac_2O/H_2SO_4 (Scheme 6). Compound (**12**) has already been prepared from 2-amino-3-quinolinecarbamide [24].

An attempt to prepare pyrimido[4,5-*b*]quinolin-4-(1H)-one (**13**) by cyclizing (**1h**) using a mixture of 10% H_2SO_4 and 88% HCOOH as reported [24] for a similar compound had failed and the starting material (**1h**) was recovered. On increasing the concentration of H_2SO_4 to 50% instead of 10% in the previous mixture and refluxing for 18 h, we obtained 2-amino-3-quinolinecarboxylic acid (**9**). Its m.p. and spectral data were identical to that prepared from (**7**) by fusion. Therefore, hydrolysis of the cyano group to carboxylic group has happened rather than cyclization to give the target compound (**13**).



i = $HCONH_2$, ii = Ac_2O / H_2SO_4, iii = Ac_2O
iv = 88% HCOOH & 10% H_2SO_4, v = 88% HCOOH & 50% H_2SO_4.

Scheme 6

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تشييد و دراسة الخصائص الطيفية لبعض مشتقات بيريميدو[٤،٥-ب] كينولين

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(قدم للنشر في ١٤٢٤/٨/٢٣هـ ؛ وقبل للنشر في ١٤٢٥/٣/٦هـ)

ملخص البحث. استخدم كل من ٢- كلورو-٣-كينولين كاربونيتريل، ٢- أمينو-٣- كينولين كاربونيتريل وحمض ٢- أكسو -٣- كينولين لتشييد بعض مشتقات بيريميدو [٤، ٥-ب] كينولين وذلك بالتحلق مع كل من اليوريا، الثيويوريا، الجوانيدين، الفورماميد و بلاماء حمض الخل. وتم تشييد بعض مشتقات البريميدين الجديدة نتيجة هذه التفاعلات التكاثفية المختلفة. تم التأكد من التركيب البنائي لمشتقات الكينولين و البيريميدوكينولين المشيدة بالوسائل الطيفية و بالأخص أطياف الكتلة و الرنين النووى المغناطيسي.