Molecules **2007**, *12*, 361-372

molecules
ISSN 1420-3049
http://www.mdpi.org

Full Paper

An Efficient Synthesis of Pyrazolo[3,4- *b*]quinolin-3-amine and Benzo[b][1,8]naphthyridine Derivatives

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Received: 24 January 2007; in revised form: 10 February 2007 / Accepted: 21 February 2007 / Published: 8 March 2007

Abstract: 2-Oxo-4-phenyl-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**10**) reacted with hydrazine hydrate, phenylisothiocyanate or benzoyl chloride to give derivatives **12**, **13** and **15**, respectively. The latter two products were treated with hydrazine hydrate to afford pyrozole[3,4-*b*]quinolines derivatives **14** and **16**, respectively. Compound **10** also reacted with acetonitrile dimer or malononitrile dimer to yield benzo[b][1,8]-naphthyridine derivatives. A single crystal X-ray crystallographic analysis was performed on compound **10**, confirming its structure.

Keywords: Hexahydroquinoline, hydrazine hydrate, urea, acetonitrile or malononitrile dimer, X-ray crystal structure.

Introduction

Tetrahydroquinolines are important building blocks in synthetic heterocyclic chemistry and their use in the preparation of pyrazolo[3,4-*b*]quinolines and benzo[b][1,8]naphthyridines derivatives has been reported recently [1-6]. Pyrazolo[3,4-*b*]quinoline derivatives are used as pharmaceutical agents and as inhibitors of oncogenic Ras [7,8]. Interesting pharmacological properties have also been associated with benzo[b][1,8]naphthyridine derivatives, which posses antitumor, trypanocidal and DNA binding properties [9,10] and are antimicrobial agents [11]. In continuation of this work, we report herein a synthesis of pyrazolo[3,4-*b*]quinoline and benzo[b][1,8]naphthyridine derivatives utilizing the hexahydroquinoline **10** as starting material.

Results and Discussion

Treatment of cyclohexanone **1** with the α,β-unsaturated nitrile derivative **2** in the presence of ammonium acetate afforded 2-oxo-4-phenyl-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**10**). The structure of **10** was assigned on the basis of its elemental analyses and x-ray crystal structure (Scheme 1, Figure 1 and Table 1).

Scheme 1

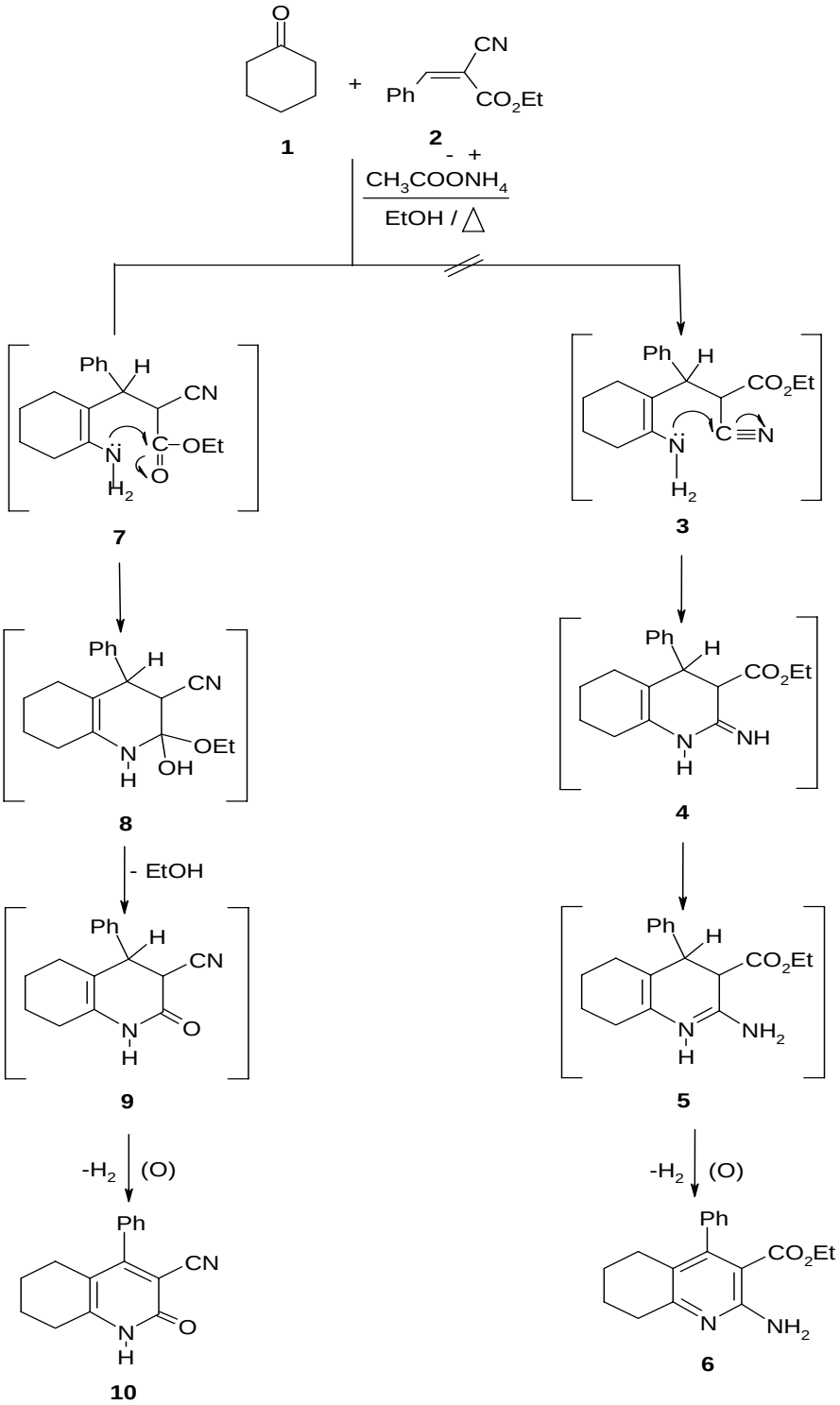


Figure 1. ORTEP diagram of compound **10.**

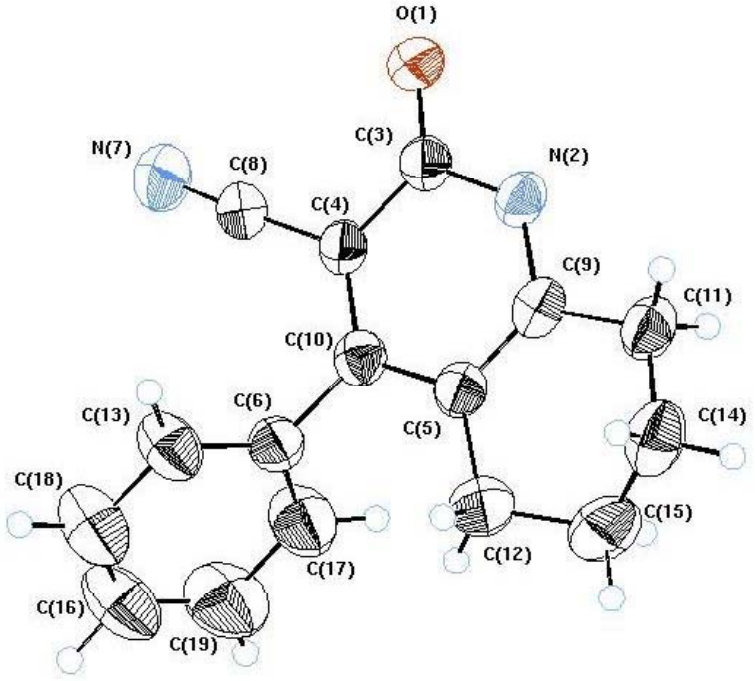
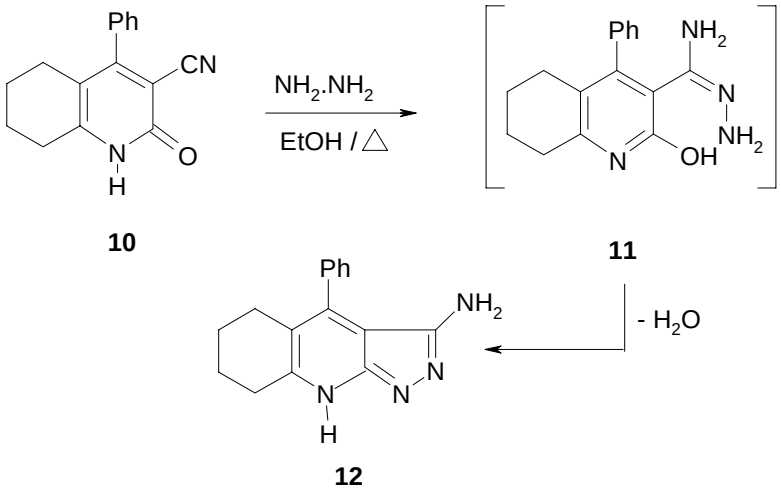


Table 1. Crystal data and structure refinement for compound **10**.

Empirical formula	$C_{16}H_{14}N_2O$
Formula weight	250.301
Temperature	298 K
Wavelength	0.71073A
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 12.7092 (6)Å b = 5.8821 (3)Å c = 18.2257 (12)Å α = 90.00° β = 101.455 (2)°
Volume	1335.36 (13)Å^3
Z, Calculated density	4, 1.240 Mg/m^3
Absorption coefficient	0.08 mm^{-1}
F(000)	236
Crystal size	1.00 x 0.22 x 0.16 mm
Diffractometer	Kappa CCD
Θ Rang (^{0})	2.910—27.485 °
Limiting indices	-16<=h<=16, -6<=k<=7, -23<=1<=22 2323<=l<=222
Reflections collected / unique	3473 / 1103 [R(int) = 0.035]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1102/ 0 / 172
Goodness-of-fit on F^2	2.291
Final R indices [I>3sigma(I)]	R_1 = 0.172, wR_2 = 0.119
R indices (all data)	R_1 = 0.051, wR_2 = 0.139
Extinction coefficient	0.046(2)
Largest diff. peak and hole	0.049 and -0.50eÅ^3

Compound **10** reacted with hydrazine hydrate in absolute ethanol to afford pyrazolo[3,4-*b*]quinoline derivative **12** through elimination of a water molecule from intermediate **11** (Scheme 2).

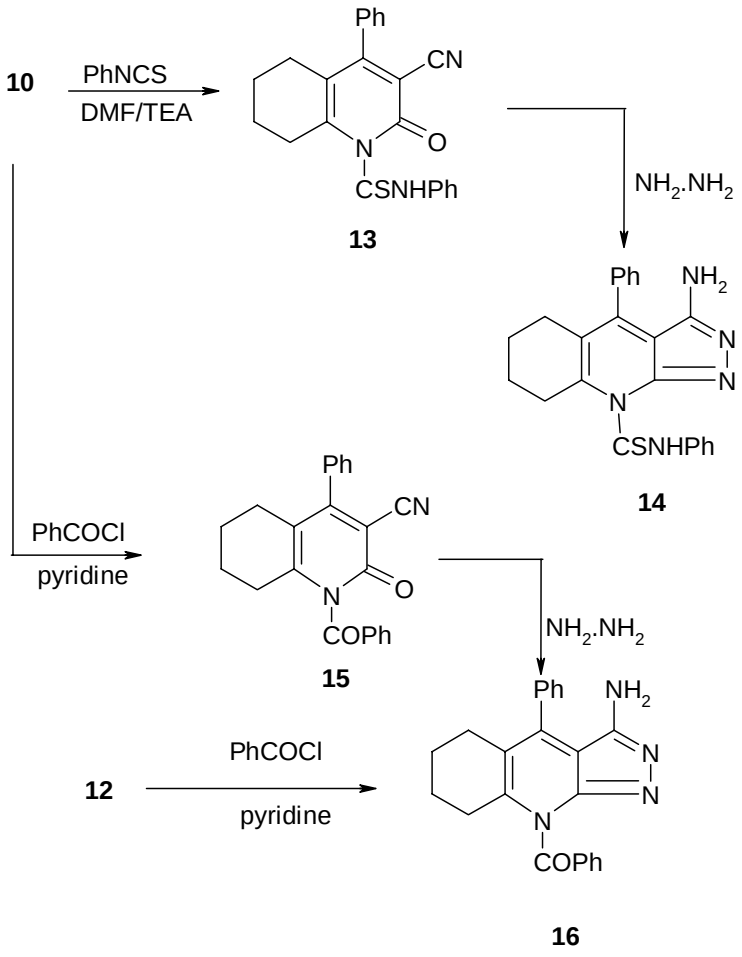
Scheme 2



10 **11** **12**

When the hexahydroquinoline **10** was treated with phenylisothiocyanate, it afforded a single product **13** (Scheme 3).

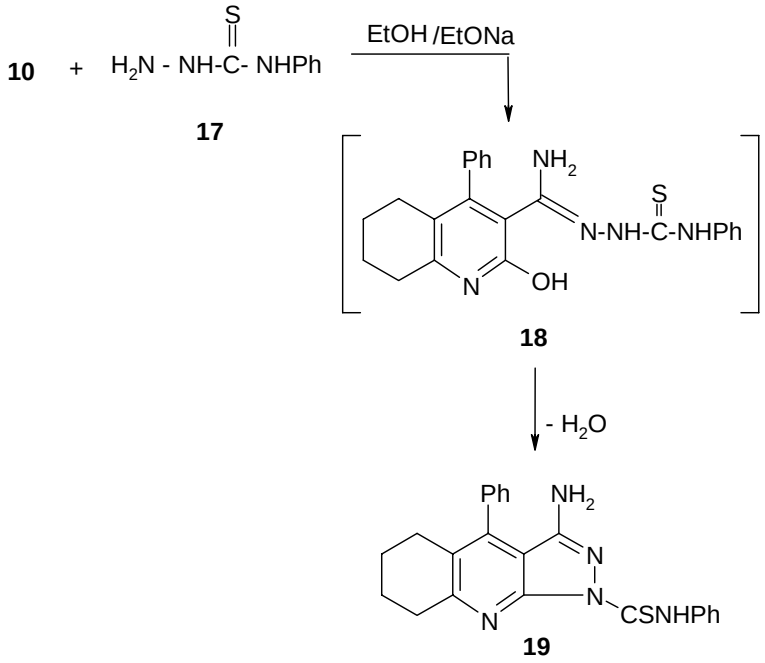
Scheme 3



13 **14** **15** **16**

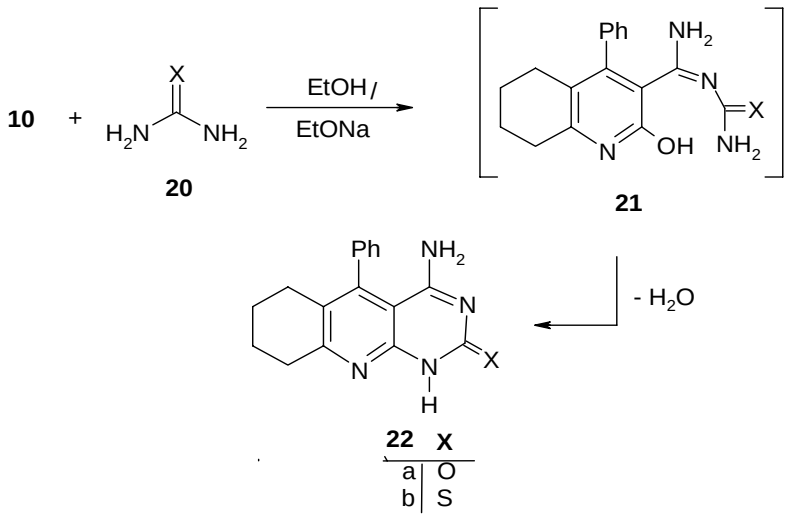
Treatment of a suspension of the latter product with hydrazine hydrate, under reflux, afforded 3-amino-*N*,4-diphenyl-5,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolin-9-carbothioamide (**14**). An alternative method for preparing compound **14** involves treating compound **12** with phenyl isothiocyanate under similar conditions. Similarly, when compound **10** was treated with benzoyl chloride, it afforded hexahydroquinaline derivative **15**. Treatment of **15** with hydrazine hydrate, under reflux, afforded 3-amino-5,6,7,8-tetrahydro-4-phenyl-pyrazolo[3,4-*b*]quinoline-9-yl)(phenyl)methanone (**16**), which can also be obtained by an independent method through treatment of compound **12** with benzoyl chloride (Scheme 3). Compound **10** reacted phenylthiosemicarbazide **17** [12] in absolute ethanol/sodium ethoxide to afford 3-amino-5,6,7,8-tetrahydro-*N*,4-diphenylpyrazolo[3,4-*b*]quinoline-1-carbothioamide (**19**) via the cyclodehydration of intermediate **18** (Scheme 4).

Scheme 4



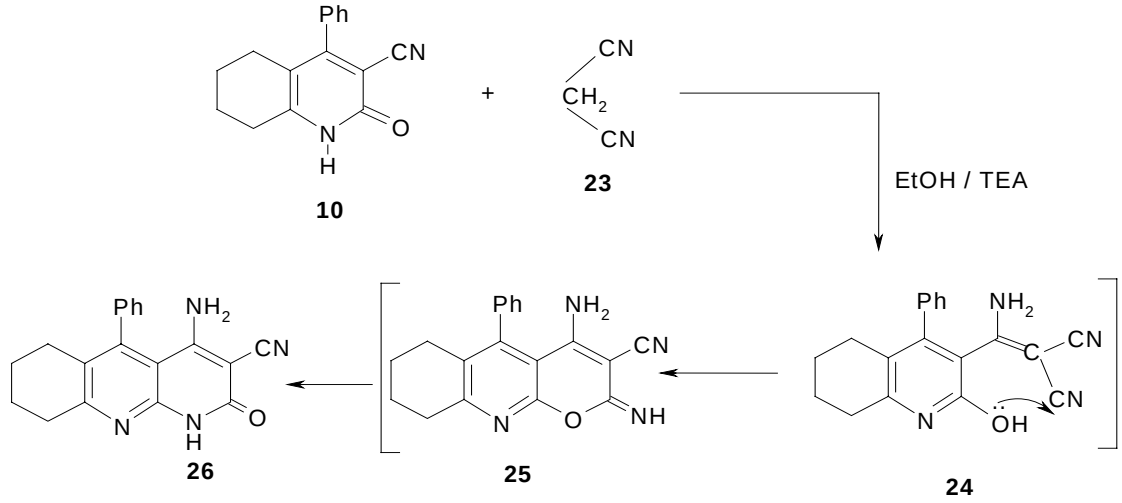
Compound **10** reacted with urea or thiourea in absolute ethanol/sodium ethoxide for 5h to afford 4-amino-5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-2(1*H*)one / -2(1*H*)thiones **22a,b** through the intermediate **21** via the elimination of a water molecule (Scheme 5).

Scheme 5



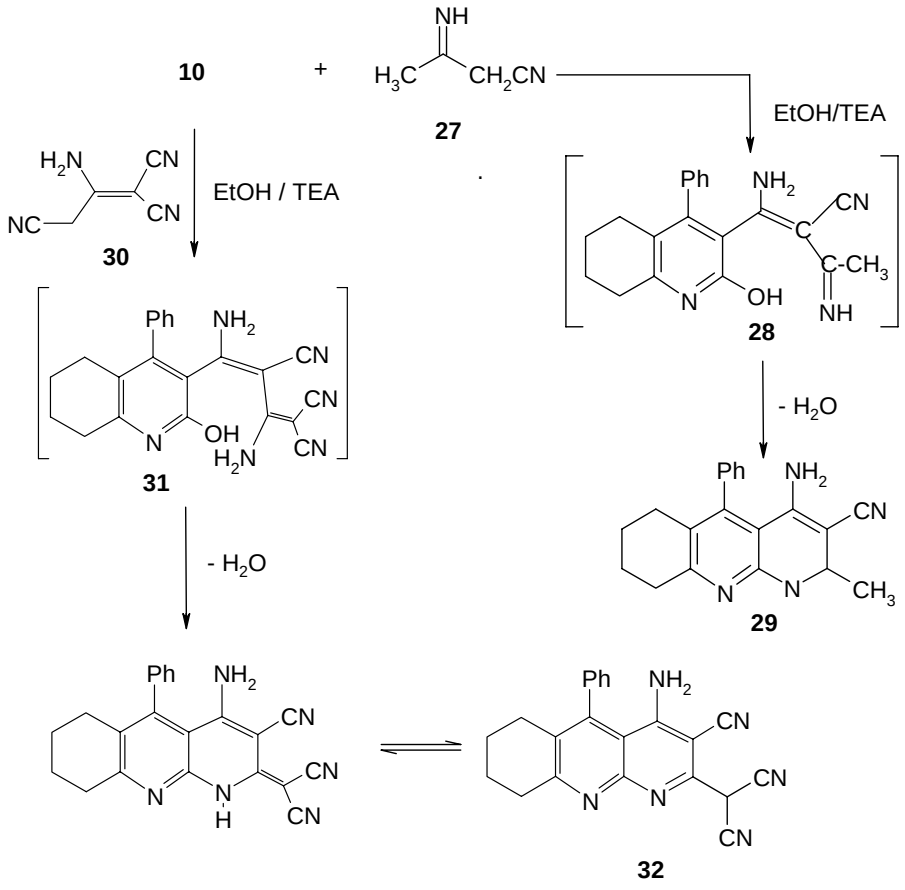
In addition, compound **10** was refluxed with malononitrile to afford 4-aminobenzo[b]-[1,8]napthyridine-3-carbonitrile (**26**) via the intermediates **24** and **25**, as confirmed by elemental analysis, ^{1}H- and ^{13}C-NMR (Scheme 6).

Scheme 6



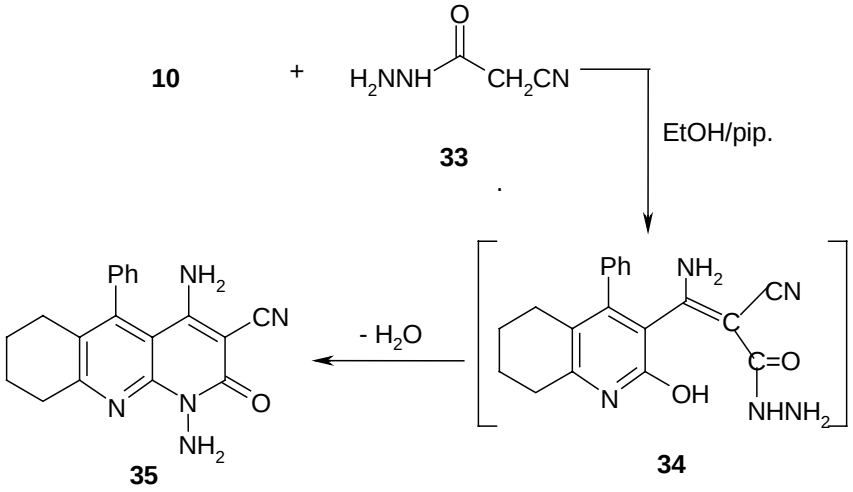
Hexahydroquinoline derivative **10** reacted with acetonitrile dimer (3-iminobutanenitrile) or malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) to afford 4-amino-benzo[b][1,8] napthyridinecarbonitrile derivatives **29** and **32**. These reactions proceed by addition of the active methylene group to the cyano group to give the intermediate **28** and **31**, which undergo cyclization via the elimination of a water molecule. The structures of the isolated product were confirmed by elemental and spectral analyses.

Scheme 7



The target ring system **35** was synthesized by reaction of **10** with cyanoacetohydrazide **33** through the intermediate **34** via elimination of a water molecule (Scheme 8).

Scheme 8



Experimental

General

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, Cairo University, Giza, Egypt. IR spectra (KBr) were recorded on Pye Unicam SP 1200 Spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 90 MHz Varian NMR Spectrometer using TMS as an internal standard and chemical shifts are expressed as δ ppm units. The homogeneity of all compounds synthesized was checked by TLC on 2.0 cm x 6.0 cm aluminum sheets recoated with silica gel 60 containing a fluorescent indicator, to a thickness of 0.25µm. Characterization data of the various compounds prepared are given in Tables 2 and 3.

2-Oxo-4-phenyl-1,2 ,5,6,7,8-hexarahydroquinoline–3–carbonitrile (**10**).

A solution of cyclohexanone (**1**, 0.01 mol) in absolute ethanol (30 mL) containing excess ammonium acetate and the arylidene derivative **2** (0.01 mol) was heated under reflux for 3-5 h. The solid material which separated during heating was collected by filtration and recrystallized from ethanol to yield the hexahydroquinoline derivative **10**.

5,6,7,8-Tetrahydro-4-phenyl-1H-pyrazolo[3,4-b]quinolin-3-amine (**12**)

A mixture of **10** (0.005 mol) and hydrazine hydrate (0.005 mol) in absolute ethanol (30 mL) was refluxed for 4 h. and the reaction mixture was left at room temperature overnight and then poured into ice/cold water to complete precipitation. The product was filtered off and recrystallized from dry benzene to give compound **12**.

3-Cyano-5,6,7,8-tetrahydro-2-oxo-N,4-diphenylquinoline-1(2H)-carbothioamide (**13**)

A mixture of **10** (0.005 mol) and phenylisothiocyanate (0.005 mol) in dimethylformamide containing a catalytic amount of triethylamine (4 drops) was refluxed for 5 h. and then left to cool to room temperature. The reaction mixture was poured into cold water for complete precipitation, then the solids were filtered off, washed with water, dried well and recrystallized from aqueous methanol to give compound **13**.

3-Amino-N,4-diphenyl-5,6,7,8-tetrahydro-pyrazolo[3,4-b]quinolin-9-carbothioamide (**14**)

A mixture of **13** (0.01 mol) and hydrazine hydrate (0.01 mol) in absolute ethanol (30 mL) was refluxed for 3 h. and the reaction mixture was left at room temperature overnight and then poured into ice/cold water to complete precipitation. The product was filtered off and recrystallized from dry benzene to give compound **14**.

(3-Cyano-5,6,7,8-tetrahydro-2-oxo-4-phenylquinoline)(phenyl)methanone (**15**)

Benzoyl chloride (0.01 mol) was added to a solution of **10** (0.01 mol) in dry pyridine (30 mL) and the mixture was refluxed on a water bath for 5 h., then left to cool to room temperature and poured into ice cold water and neutralized by diluted hydrochloric acid for complete precipitation. The separated material was collected by filtration, washed with water, dried well and recrystallized from acetic acid to yield compound **15**.

(3-Amino-5,6,7,8-tetrahydro-4-phenylpyrazolo[3,4-b]quinoline-9-yl)(phenyl)methanone (**16**)

A mixture of **15** (0.01 mol) and hydrazine hydrate (0.01 mol) in absolute ethanol (30 mL) was refluxed for 3 h. and the reaction mixture was left at room temperature overnight and then poured into ice/cold water to complete precipitation. The product was filtered off and recrystallized from dry benzene to give compound **16.**

General procedure for the synthesis of 3–amino–5,6,7,8-tetrahydro-N,4-diphenylpyrazolo[3,4-b]-quinolin-1-carbothioamide (**19**), *4-amino-6,7,8,9-tetrahydro-5-phenylpyrimido[4,5-b]quinolin-2(1H)-one* (**22a**) *and 4-amino-6,7,8,9-tetrahydro-5-phenylpyrimido[4,5-b]quinolin-2(1H)thione* (**22b**).

A mixture of **10** (0.005 mol) and phenylthiosemicarbazide (0.005 mol), urea (0.005 mol) or thiourea (0.005 mol) in absolute ethanol (20 mL) containing sodium ethoxide (0.005 mol) was refluxed for 6 h. The reaction mixture was left to cool to room temperature, then poured into ice cold water (50 mL) and neutralized with dilute hydrochloric acid; the separated material was filtered off and recrystallized from ethanol to give compounds **19**, **22a** or **22b.**

4-Amino-1,2,6,7,8,9-hexahydro-2-oxo-5-phenyl-benzo[b][1,8]naphthyridin-3-carbonitrile (**26**).

To a solution of **10** (0.005 mol) in absolute ethanol (30 mL), triethylamine(5 mL) malononitrile (0.005 mol) was added and the reaction mixture was refluxed for 6 h., then left to cool to room temperature, poured into cold water and neutralized with diluted hydrochloric acid to complete precipitation. The solid obtained was filtered off, washed with water, dried well and recrystallized from methanol to give compound **26**.

General procedure for the synthesis of 4-amino-6,7,8,9-tetrahydro-2-methyl-5-phenylbenzo[b][1,8]-naphthyridin-3-carbonitrile (**29**) *and 4-amino-2-(dicyanomethylene)-1,2,6,7,8,9-hexahydro-5-phenyl-benzo[b][1,8] naphthyridin-3-carbonitrile* (**32**).

An equimolar mixture of **10** (0.005 mol) and acetonitrile dimmer (3-iminobutanenitrile, **27**, 0.005 mol) or malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile, **30,** 0.005 mol) in absolute ethanol (30 mL) in the presence of a few drops of triethylamine (4 drops) was refluxed for 6 h. The reaction mixture was left to cool and poured into cold water for complete precipitation. The separated solid was filtered off, washed with water, dried well and recrystallized from ethanol to give compounds **29** or **32**.

1,4-Diamino-1,2,6,7,8,9-hexahydro-2-oxo-5-phenylbenzo[b][1,8] naphthyridin-3-carbonitrile (**35**)

A few drops of pipridine were added to a solution of **10** (0.005 mol) and cynanoacetohydrazide (0.005 mol) in absolute ethanol (30 mL) and the reaction mixture was refluxed for 5 h., then left to cool. The product was filtered off, washed with water, dried well and recrystallized from ethanol to give compound **35**.

Table 2 Physical properties and elemental analyses of the new compounds.

Compd.	M.P.°C	Formula (mw)	Analysis % Calcd. (Found)				
			C	H	N	S	Cl
10	275	$C_{16}H_{14}N_2O$ (250.30)	76.78 (77.02)	5.64 (5.82)	11.19 (11.46)	–	–
12	225	$C_{16}H_{16}N_4$ (264.33)	72.70 (73.00)	6.10 (6.46)	21.20 (21.49)	–	
13	240	$C_{23}H_{19}N_3SO$ (385.47)	71.66 (71.89)	4.97 (5.04)	10.90 (11.15)	8.32 (8.45)	–
14	192	$C_{23}H_{21}N_5S$ (399.50)	69.14 (69.39)	5.29 (5.56)	17.52 (17.70)	8.02 (8.34)	–
15	216	$C_{23}H_{18}N_2O_2$ (354.41)	77.95 (78.24)	5.12 (5.47)	7.90 (8.04)	–	–
16	290	$C_{23}H_{20}N_4O$ (368.44)	74.98 (75.27)	5.47 (5.79)	15.21 (15.77)	–	–

Table 2. Cont.

Compd.	M.P.°C	Formula (mw)	Analysis % Calcd. (Found)				
			C	H	N	S	Cl
19	223	$C_{23}H_{21}N_5S$ (399.50)	69.15 (69.44)	5.30 (5.43)	17.53 (17.81)	8.03 (8.32)	–
22a	207~209	$C_{17}H_{16}N_4O$ (292.34)	69.85 (69.79)	5.52 (5.62)	19.16 (19.53)	–	–
22b	185~186	$C_{17}H_{16}N_4S$ (308.41)	66.21 (66.74)	5.23 (5.40)	18.17 (18.21)	10.40 (10.62)	–
26	167~168	$C_{19}H_{16}N_4O$ (316.37)	72.14 (72.33)	5.10 (5.14)	17.71 (17.87)	–	–
29	198	$C_{20}H_{18}N_4$ (314.39)	76.41 (77.73)	5.77 (5.73)	17.82 (17.97)	–	–
32	215	$C_{22}H_{16}N_6$ (364.41)	72.51 (72.84)	4.43 (4.68)	23.06 (23.18)	–	–
35	178	$C_{19}H_{17}N_5O$ (331.38)	68.87 (69.01)	5.17 (5.29)	21.13 (21.49)	–	–

Table 3 IR , ^{1}H- and ^{13}C-NMR of the new compounds.

Compd.	IR (cm^{-1})	^{1}H and ^{13}C-NMR (δ, ppm)
10	3226 (NH), 2215 (CN), 1717 (CO).	1.64-1.98 (m, 8H, $4CH_2$); 7.13-7.35 (m, 5H, Ar-H). 8.10 (s, 1H, NH).
12	3424-3345 (NH_2), 3166 (NH), 1650 (C=N).	1.62-2.84 (m, 8H, $4CH_2$); 5.81 (s, 2H, NH_2), 7.20-7.44 (m, 5H, Ar-H), 13.71 (s, 1H, NH).
13	3266 (NH), 2215 (CN), 1723 (CO), 1346 (CS).	1.64-2.83 (m, 8H, $4CH_2$); 4.12 (s, H, NH); 7.21-7.63 (m, 10H, Ar-H).
14	3424-3345 (NH_2), 3266 (NH), 1346(CS).	1.64-2.82 (m, 8H, $4CH_2$); 2.14 (s, 2H, NH_2); 4.13 (1s,1H, NH), 6.42-7.41 (m, 10H, Ar-H).
15	2215 (CN), 1723, 1672 (2CO).	-----
16	3408-3320 (NH_2), 1672 (CO).	1.64-2.84 (m, 8H, $4CH_2$); 5.41 (s, 2H, NH_2); 7.13-7.52 (m, 10H, Ar-H).
19	3421-3307 (NH_2), 3126 (NH), 1346 (CS).	-----
22a	3419-3303 (NH_2), 3126 (NH), 1692 (C=O).	1.64-2.98 (m, 8H, $4CH_2$); 5.41 (s, 2H, NH_2), 7.13-7.35 (m, 5H, Ar-H); 8.12 (s, 1H, NH).
22b	3419-3303 (NH_2), 3146 (NH), 1363 (CS).	1.64-2.98 (m, 8H, $4CH_2$); 5.42 (s, 2H, NH_2), 7.23-7.45 (m, 5H, Ar-H); 8.12 (s, 1H, NH).

Table 3. Cont.

Compd.	IR (cm^{-1})	^{1}H and ^{13}C-NMR (δ, ppm)
26	3419-3303 (NH_2), 3146 (NH), 2215 (CN), 1707 (C=O).	^{1}H: 1.64-2.96 (m, 8H, $4CH_2$); 5.41 (s, 2H, NH_2), 7.14-7.30 (m, 5H, Ar-H); 8.01 (s, 1H, NH). ^{13}C: 22.6, 23.5, 25.2, 31.5 ($4\underline{C}H_2$); 80.34 (<u>C</u>-CN); 113.6 (<u>C</u>3-quinoline); 115.7 (<u>C</u>N); 124.4 (C=<u>C</u>-N); 127.3, 127.3, 129.5, 129.5, 129.5, 136.4 (Ph), 147.6 (<u>C</u>-2-quinoline); 149.4 (<u>C</u>-4-quinoline), 156.2 (=<u>C</u>-N=), 169.2 (<u>C</u>=O); 176.4 (=<u>C</u>-NH_2).
29	3319-3322 (NH_2), 2217(CN), 1661 (C=N).	1.64-2.88 (m, 8H, $4CH_2$); 2.56(s,3H,CH_3), 4.21(s, 2H, NH_2); 7.13-7.46 (m, 5H, Ar-H).
32	3419-3303 (NH_2), 3146 (NH), 2215, 2217 (CN).	-----
35	3419-3303 (NH_2), 2228 (CN), 1707 (C=O), 1631 (C=N).	1.61-2.85 (m, 8H, $4CH_2$), 2.15 (s, 2H, NH_2), 2.25 (s, 2H, NH_2), 7.21-7.45 (m, 5H, Ar-H).

X-ray crystallography [13]

X-ray quality crystals of the title compound **10** were obtained by slow crystallization from dimethyl sulfoxide. Experimental data is summarized in Table 1. The data were collected with the maXus computer programs on a Bruker Nonius instrument [14-18].

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Sample availability: Available from the author.

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