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On The Chemistry of Cinnoline IV [1]. Synthesis and Reactions of (4-Aminocinnolin-3-yl)-aryl-methanones

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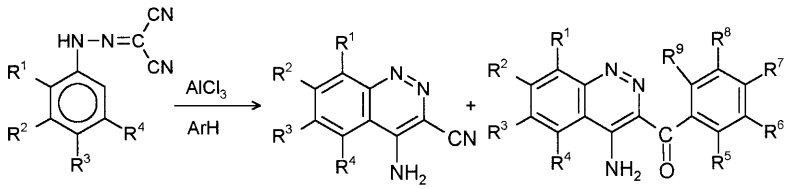
Summary. The synthesis of a series of disubstituted (4-aminocinnolin-3-yl)-aryl-methanones from aryl-hydrazonomalononitrile in a one-step procedure is described. Cyclocondensation of (4-amino-6,8-dimethyl-cinnolin-3-yl)-phenyl-methanone with malononitrile, diethylmalonate, and dimethylacetamide-dimethylacetal gave the corresponding pyrido[3,2-*c*]cinnoline derivatives. Treatment of (4-amino-6,8-dimethyl-cinnolin-3-yl)-phenyl-methanone with triethyl-orthoacetate under reflux readily afforded the corresponding imidoester which underwent cyclization to a pyrido[3,2-*c*]cinnoline derivative. This starting compound could also be annelated to the corresponding 1,2-dihydro-4-aryl-2-oxo-pyrido[3,2-*c*]cinnoline derivatives *via* the (4-acetamidocinnolin-3-yl)-aryl-methanones. Chemical and spectroscopic evidences for the structures of the new compounds are presented. The effect of three of the compounds against sixty cancer types was tested.

Keywords. Cycloadditions; Hydrazones; Cinnolines; Pyridines; Antitumor activity.

Introduction

Derivatives of cinnolines and their benzo and heterocyclic analogs exhibit biological activity in various areas, including antihypertensive, antihrombotic, antitumor, antisecretory [2–4], and bactericidal activities [5]. 4-Aminocinnolines have recently become of importance due to their antibacterial, antihistaminic, and insecticidal properties [6, 7]. Moreover, in recent years these derivatives have been extensively utilized as intermediates for the synthesis of fused cinnolines of potential biological activity [8, 9]. Some 4-amino-3-cinnolinecarboxylic acid derivatives have been described as nonbenzodiazepine anxiolytic agents or benzodiazepine receptor antagonists [10, 11]. These pharmacological properties and interest in the chemistry of cinnolines [11, 12] prompted the synthesis of a number of new (4-aminocinnolin-3-yl)-*p*-tolyl-methanones as synthons for the preparation of new pyrido[3,2-*c*]cinnolines with respect to a projected investigation of their utility as pharmacological agents. Various biological activities, *e.g.* an interesting diuretic effect [13], have been observed with derivatives of pyrido[2,3-*d*]pyridazines. The method described provides a potential starting point for the synthesis of many new pyrido[3,2-*c*]cinnoline derivatives.

Results and Discussion



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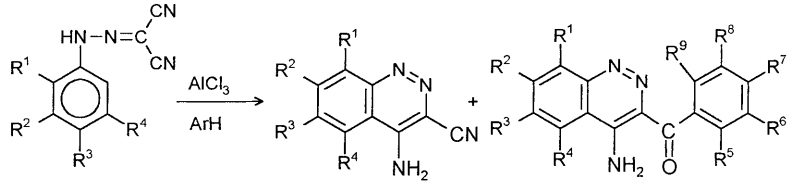
The results of experiments designed to explore the scope and the limitations of the *Gewald* procedure [14] as a synthetic method for the formation of (cinnolin-3-yl)-aryl-methanones bearing various substituents **3a–q** are reported. The aim of this investigation is to study the effect of the substituent at the aryl group during the cyclization of the aryl hydrazonomalononitriles **1a**,**h**,**o**,**q** to obtain the new and potentially useful substituted (cinnolin-3-yl)-aryl-methanones **3a–q**. Therefore, **1a**,**h**,**o**,**q** were synthesized in good yields by treatment of malononitrile with the diazonium salts of the corresponding aniline derivatives (2,4-dimethylaniline, 2,5-dimethylaniline, 2,3-dimethylaniline, and 4-bromo-3-methylaniline). The hydrazone structure was confirmed by their ^{1}H NMR spectra which included the broad



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	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
a	CH_3	H	CH_3	H	H	H	H	H	H
b	CH_3	H	CH_3	H	H	H	CH_3	H	H
c	CH_3	H	CH_3	H	H	H	C_2H_5	H	H
d	CH_3	H	CH_3	H	H	CH_3	CH_3	H	H
e	CH_3	H	CH_3	H	CH_3	H	CH_3	H	H
f	CH_3	H	CH_3	H	CH_3	H	H	CH_3	H
g	CH_3	H	CH_3	H	CH_3	H	CH_3	H	CH_3
h	CH_3	H	H	CH_3	H	H	H	H	H
I	CH_3	H	H	CH_3	H	H	CH_3	H	H
j	CH_3	H	H	CH_3	H	H	C_2H_5	H	H
k	CH_3	H	H	CH_3	H	CH_3	CH_3	H	H
l	CH_3	H	H	CH_3	CH_3	H	CH_3	H	H
m	CH_3	H	H	CH_3	CH_3	H	H	CH_3	H
n	CH_3	H	H	CH_3	CH_3	H	CH_3	H	CH_3
o	CH_3	CH_3	H	H	H	H	CH_3	H	H
p	H	CH_3	Br	H	CH_3	H	CH_3	H	H
q	H	H	Br	CH_3	CH_3	H	CH_3	H	H

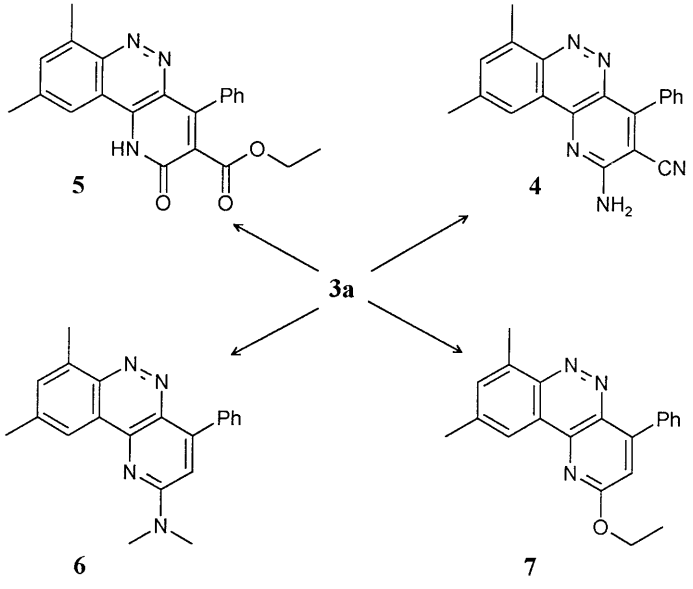
Scheme 1

signal of the NH group (exchangeable with D_2O, 9.6 ppm). IR spectra (KBr) of **1** showed the characteristic absorption bands for NH groups at 3350 to 3198 cm^{-1} and for a cyano group at 2218 cm^{-1}. The (4-aminocinnolin-3-yl)-phenyl-methanones **3a** and **3h** were readily obtained *via* cyclization of **1** in presence of $AlCl_3$ in benzene under reflux conditions (Scheme 1).

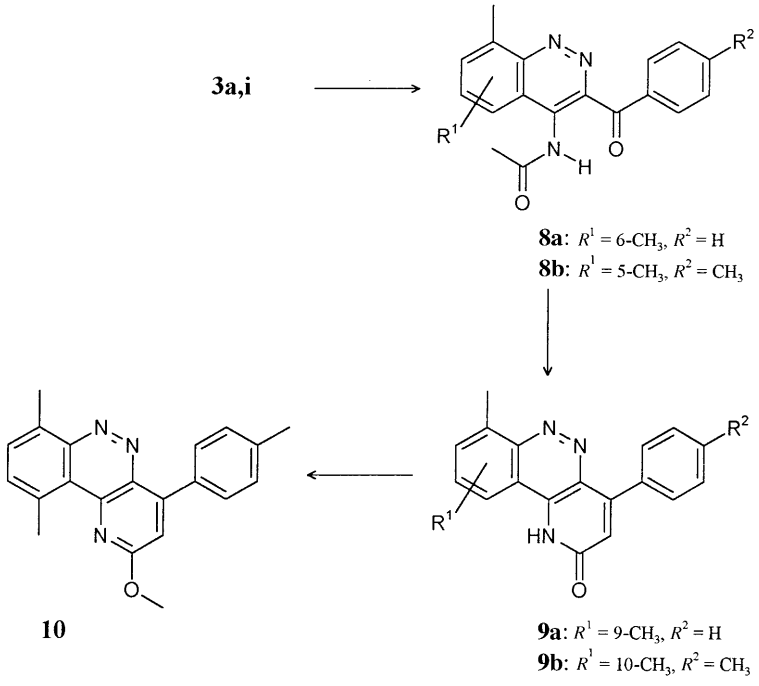
Variation of the solvent during the cyclization of aryl-hydrazono-malononitriles **1** led to the new and useful substituted (4-aminocinnolin-3-yl)-aryl-methones **3a–q** in particularly excellent yields. Thus, toluene, ethyl benzene, *o*-xylene, *m*-xylene, *p*-xylene, and 1,3,5-trimethylbenzene yielded under the same conditions *via* intra-cyclization of **1a** and **1h** compounds **3b–g** and **3i–q** in excellent yields. However, compounds **2a** and **2h** were not observed (Scheme 1). Furthermore, certain solvents such as carbon disulfide, dichloromethane, carbon tetrachloride, pyridine, and thiophene as well as solvent-free conditions did not lead to the cyclization of **1a**, irrespective of the temperature employed. In most of these cases, **1** could be partially recovered.

The proposed mechanism involves an intramolecular *Friedel-Crafts* cyclization gives **2a** and **2h** first. Then, condensation of the cyano group at position 3 of **2** with the nonpolar aromatic solvents mentioned above in presence of the *Lewis* acid yields the corresponding ketones **3a–q** in a *Hoesch*-type reaction [15].

Having available the novel ketones **3** as readily accessible starting materials, synthesis of bi- and tricyclic systems containing a pyridazine subunit [16–17] was attempted. Cyclocondensation of (4-amino-6,8-dimethylcinnolin-3-yl)-phenyl-methanone **3a** with malononitrile, diethylmalonate, and dimethylacetamide-dimethylacetal gave the pyrido[3,2-*c*]cinnoline derivatives **4–6**. Treatment of **3a** with triethyl-orthoacetate under reflux readily afforded the corresponding imidoester which underwent cyclization to the pyrido[3,2-*c*]cinnoline derivative **7** in dimethylformamide in presence of potassium carbonate at reflux temperature (Scheme 2).



Scheme 2



Scheme 3

Treatment of the (4-aminocinnolin-3-yl)-*p*-tolyl-methanones **3a**,**i** with acetic anhydride under reflux readily afforded the 4-N-acetylated ketones **8a**,**b** which underwent cyclization to the pyrido[3,2-*c*]cinnoline derivatives **9a**,**b** in dimethylformamide in presence of potassium carbonate at reflux temperature. Interestingly, **9b** was regioselectivity O-methylated in position 2 upon treatment with CH_3I/KOH to yield **10**. The alternative N-position 1 seems shielded due to steric factors. Nevertheless, this result is one of the rare exceptions [12] of the *Kornblum* rule (Scheme 3).

Compounds **2a**,**h** and **3a**–**q** were tested for antimicrobial activity using the agar diffusion method [18] against representatives of gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*E. coli* and *Pseudomones aeruginosa*). A concentration of $0.06\,mg \cdot cm^{-3}$ showed good inhibition zones of 10–15 mm, similar to those obtained with streptomycin.

The effects of **2a**, **3b**, and **3g** were tested against several cancer lines (Table 1) at a minmum of five concentrations at 10-fold dilutions. A 48 hour continuous drug exposure protocol was used, and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The results shown in Table 1 revealed that, depending on the functional group on the cinnoline derivatives, the compounds showed varying growth depression. Thus, the cyano group in **2a** is less effective compared to the carbonyl groups in compounds **3b** and **3g**.

Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer; chemical

Table 1. Effect of **2a**, **3b**, and **3g** against several cancer lines

Panel/Cell line	% Growth in presence of **2a** $^{10}\log c$ (mg/cm^3)		% Growth in presence of **3a** $^{10}\log c$ (mg/cm^3)		% Growth in presence of **3g** $^{10}\log c$ (mg/cm^3)	
	−5.0	−4.0	−5.0	−4.0	−5.0	−4.0
Leukemia						
MOLT-4	112	103	108	4	83	33
RPMI-8226	105	92	94	11	64	29
SR	113	102	115	4	70	18
Non-small cell lung cancer						
A549/ATCC	99	91	98	14	76	5
HOP-62	110	97	74	12	67	−63
HOP-92	106	86	83	−38	44	−17
NCI-H226	84	67	80	18	73	−32
NCI-H23	112	89	82	2	75	2
NCI-H322M	100	90	85	22	76	−24
Colon cancer						
COLO 205	90	80	97	−77	81	−87
HCT-116	86	82	92	−16	52	−87
HT29	97	81	78	11	93	−12
KM12	97	82	80	−16	76	−46
SW-620	91	82	105	16	78	12
CNS cancer						
SF-268	126	117	104	6	98	28
SNB-19	97	91	93	19	90	18
U251	126	98	103	5	86	7
Melanoma						
LOX IMVI	103	97	100	2	80	−67
M14	108	95	96	19	69	−61
SK-MEL-2	136	107	85	−61	76	−75
SK-MEL-28	86	88	111	16	72	−24
SK-MEL-5	78	67	88	−83	72	−95
UACC-257	101	89	94	−4	89	22
UACC-62	106	70	79	−42	69	−18
Ovarian cancer						
IGROVI	100	75	80	10	69	−34
OVCAR-5	76	93	93	17	60	11
Renal cancer						
786-0	96	91	85	13	61	−59
ACHN	111	95	97	−22	79	
CAKI-1	92	80	91	4	74	−10
Prostate cancer						
PC-3	100	94	102	−29	73	−24
DU-145	102	82	89	−16	94	−8
Breast cancer						
NCI/ADR-RES	105	116	85	−20	90	−13
MDA-MB-231/ATCC	101	101	78	−29	70	−17
MDA-MB-435	107	93	89	−25	68	−23
BT-549	88	78	73	−12	103	37

shifts are given in ppm relative to internal *TMS* at 295 K. IR spectra were obtained on Biorad FT-IR-45 instrument. All experiments were carried out with exclusion of moisture. For all newly synthesized compounds satisfactory elemental analyses were obtained.

Preparation of aryl-hydrazonomalononitriles (**1**)

To a well stirred solution of 6.66 g malononitrile (100 mmol) in 130 cm^3 EtOH and 20 cm^3 H_2O containing 10 g CH_3COONa, the diazonium salt (100 mmol) prepared in the usual way from the corresponding aniline was added gradually with stirring during 20 min at 0–5°C. The product was filtered, washed with H_2O, dried, and recrystallized from the given solvent.

2,4-Dimethylphenyl-hydrazonomalononitrile (**1a**; $C_{11}H_{10}N_4$)

Prepared from 2,4-dimethylaniline; crystallization from EtOH gave fine orange crystals (95%); m.p.: 96°C; IR (KBr): $\bar{\nu} = 3350$ br, 3199, 2920 br, 2218, 1610, 1532, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.33 (s, CH_3), 2.36 (s, CH_3), 7.03 (s, $1H_{ar}$), 7.08 (d, $1H_{ar}$), 7.38 (d, $1H_{ar}$), 9.60 (br, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 26.00 (CH_3), 30.48 (CH_3), 96.31 (CH), 117.00, 121.00, 125.98, 133.88, 138.21, 141.50, 144.90, 146.29 (aryl, 2CN) ppm.

2,5-Dimethylphenyl-hydrazonomalononitrile (**1h**; $C_{11}H_{10}N_4$)

Prepared from 2,5-dimethylaniline; crystallization from MeOH gave fine yellow crystals (98%); m.p.: 158–160°C; IR (KBr): $\bar{\nu} = 3350$ br, 3198, 2921, 2218, 1608, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.35 (s, CH_3), 2.36 (s, CH_3), 6.99 (d, $J = 7.7$ Hz, $1H_{ar}$), 7.08 (d, $J = 7.7$ Hz, $1H_{ar}$), 7.34 (s, $1H_{ar}$), 9.65 (br, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 25.59 (CH_3), 30.75 (CH_3), 96.76 (CH), 117.62, 121.78, 126.26, 130.90, 137.05, 140.81, 146.80, 147.71 (aryl, 2CN) ppm.

2,3-Dimethylphenyl-hydrazonomalononitrile (**1o**; $C_{11}H_{10}N_4$)

Prepared from 2,3-dimethylaniline; crystallization from EtOH gave fine yellow crystals (98%); m.p.: 198°C; IR (KBr): $\bar{\nu} = 3350$ br, 3198, 2920 br, 2218, 1608, 1474 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.29 (s, CH_3), 2.36 (s, CH_3), 7.08 (d, $J = 7.4$ Hz, $1H_{ar}$), 7.17–7.25 (t, $1H_{ar}$), 7.38 (d, $J = 8.0$ Hz, $1H_{ar}$), 9.69 (br, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 12.27 (CH_3), 20.28 (CH_3), 87.21 (CH), 108.12, 112.18, 114.54, 123.16, 127.18, 128.33, 137.49, 138.26 (aryl, 2CN) ppm.

4-Bromo-3-methyl-phenyl-hydrazonomalononitrile (**1q**; $C_{10}H_7BrN_4$)

Prepared from 4-bromo-3-methylaniline; crystallization from ethyl acetate gave fine yellow crystals (80%); m.p.: 190°C; IR (KBr): $\bar{\nu} = 3343$ br, 3195, 2218, 1610, 1480, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.44 (s, CH_3), 6.99 (dd, $J = 8.6$ Hz, $J = 2.4$ Hz, $1H_{ar}$), 7.21 (s, $1H_{ar}$), 7.55 (d, $J = 8.6$ Hz, $1H_{ar}$), 9.66 (br, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 32.72 (CH_3), 96.91 (CH), 117.56, 121.48, 124.38, 127.49, 132.06, 143.25, 148.29, 149.71 (aryl, 2CN) ppm.

General procedure for the preparation of 4-aminocinnolin-3-carbonitrile and (4-aminocinnolin-3-yl)-p-tolyl-methanone derivatives

A mixture of 10 mmol **1** and 2.50 g $AlCl_3$ (0.04 mmol) in 150 cm^3 of a nonpolar aromatic solvent (benzene, toluene, ethylbenzene, *o*-xylene, *m*-xylene, *p*-xylene, 1,3,5-trimethylbenzene) was heated under reflux for 5 h with stirring and then allowed to cool to room temperature. The resulting product

was poured on 500 cm^3 cold H_2O and left for 2 h. The resulting solid product was collected by filtration, washed with petroleum ether (40–60°), and crystallized from the solvent given.

4-Amino-6,8-dimethylcinnolin-3-carbonitrile (**2a**; $C_{11}H_{10}N_4$)

Prepared from 2,4-dimethylaniline; crystallization from petroleum ether gave greenish yellow crystals (33%); m.p.: 189°C; IR (KBr): $\bar{\nu}$ = 3459, 3319, 3199, 2919, 2217, 1641, 1571, 1532, 1502, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.57 (s, CH_3), 2.95 (s, CH_3), 5.54 (br, NH_2), 7.47 (s, $1H_{ar}$), 7.57 (s, $1H_{ar}$) ppm.

4-Amino-5,8-dimethylcinnolin-3-carbonitrile (**2h**; $C_{11}H_{10}N_4$)

Prepared from 2,5-dimethylaniline; crystallization from EtOH gave fine yellow crystals (35%); m.p.: 305–306°C; IR (KBr): $\bar{\nu}$ = 3453, 3329 br, 3198, 2219, 1638, 1572, 1532, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.91 (s, CH_3), 2.96 (s, CH_3), 5.80 (br, NH_2), 7.36 (d, J = 7.3 Hz, $1H_{ar}$), 7.58 (d, J = 7.9 Hz, $1H_{ar}$) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 2.72 (s, CH_3), 2.84 (s, CH_3), 7.30 (br, NH_2), 7.38 (d, J = 7.2 Hz, $1H_{ar}$), 7.60 (d, J = 7.2 Hz, $1H_{ar}$) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 28.03 (CH_3), 33.00 (CH_3), 124.10, 127.40, 138.85, 140.30, 141.41, 142.76, 157.14, 157.78 (aryl, CN) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-phenyl-methanone (**3a**; $C_{17}H_{15}N_3O$)

Prepared from **1a**; crystallization from ethyl acetate gave cream white crystals (47%); m.p.: > 330°C; IR (KBr): $\bar{\nu}$ = 3340 br, 3131, 2974, 1631, 1606, 1566, 1526, 1474 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.58 (s, CH_3), 2.97 (s, CH_3), 5.75 (br, NH), 7.45–7.56 (m, $5H_{ar}$), 8.05 (d, J = 8.0 Hz, $2H_{ar}$) ppm; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 200 MHz): 2.48 (s, CH_3), 2.75 (s, CH_3), 7.46–7.49 (m, $3H_{ar}$), 7.57 (s, $1H_{ar}$), 7.84 (d, J = 8.2 Hz, $2H_{ar}$), 8.26 (s, $1H_{ar}$), 9.42 (br, NH_2) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 27.64 (CH_3), 31.65 (CH_3), 125.39, 126.15, 135.43, 137.35, 140.44, 141.09, 142.89, 144.52, 148.12, 148.54, 149.19, 154.48, 154.84 (aryl), 206.96 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-p-tolyl-methanone (**3b**; $C_{18}H_{17}N_3O$)

Prepared from **1a**; crystallization from *n*-propanol gave yellowish white crystals (89%); m.p.: 336–337°C; IR (KBr): $\bar{\nu}$ = 3337 br, 3256, 3125, 2973, 2920, 1630, 1606, 1566, 1526, 1474, 1422, 1410, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.24 (s, CH_3), 2.62 (s, CH_3), 2.94 (s, CH_3), 6.87 (d, J = 7.9 Hz, $2H_{ar}$), 7.54 (s, $1H_{ar}$), 7.56 (d, J = 7.9 Hz, $2H_{ar}$), 7.82 (s, $1H_{ar}$), 10.10 (br, NH), 10.95 (br, NH) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 2.40 (s, CH_3), 2.48 (s, CH_3), 2.75 (s, CH_3), 7.31 (d, J = 7.9 Hz, $2H_{ar}$), 7.68 (s, $1H_{ar}$), 7.79 (d, J = 7.9 Hz, $2H_{ar}$), 8.27 (s, $1H_{ar}$), 9.19 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 27.39 (CH_3), 31.21 (CH_3), 31.46 (CH_3), 126.40, 129.70, 135.45, 138.39, 138.84, 140.71, 142.96, 144.44, 145.89, 149.12, 152.30, 155.61 (aryl), 206.00 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-(4-ethylphenyl)-methanone (**3c**; $C_{18}H_{17}N_3O$)

Prepared from **1a**; crystallization from EtOH gave faint yellowish white crystals (83%); m.p.: 275–276°C; IR (KBr): $\bar{\nu}$ = 3344, 3131, 3032, 2932, 1630, 1610, 1560, 1528, 1474 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 1.19–1.27 (t, J = 7.6 Hz, CH_3), 2.49 (s, CH_3), 2.69 (q, J = 7.6 Hz, CH_2), 2.75 (s, CH_3), 7.36 (d, J = 8.0 Hz, $2H_{ar}$), 7.74 (s, $1H_{ar}$), 7.83 (d, J = 8.0 Hz, $2H_{ar}$), 8.32 (s, $1H_{ar}$), 9.35 (br, NH_2) ppm; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 200 MHz): 1.17–1.25 (t, J = 7.6 Hz, CH_3), 2.48 (s, CH_3), 2.62–2.69 (q, J = 7.6 Hz, CH_2), 2.76 (s, CH_3), 7.23 (d, J = 8.0 Hz, $2H_{ar}$), 7.55 (s, $1H_{ar}$), 7.80 (d, J = 8.0 Hz, $2H_{ar}$), 8.23 (s, $1H_{ar}$, 9.30 (br, NH_2) ppm; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 1.21–1.28 (t,

$J = 7.6$ Hz, CH_3), 2.58 (s, CH_3), 2.61–2.68 (q, $J = 7.6$ Hz, CH_2), 2.96 (s, CH_3), 7.22–7.27 (m, $3H_{ar}$), 7.54 (s, $1H_{ar}$), 7.80 (br, NH), 7.92 (d, $J = 8.0$ Hz, $2H_{ar}$) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 25.46 (CH_3), 27.32 (CH_3), 31.44 (CH_3), 38.28 (CH_2), 126.78, 130.00, 135.43, 137.35, 140.78, 142.91, 145.64, 146.71, 149.39, 150.84, 157.49, 158.64 (aryl), 204.30 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-(3,4-dimethylphenyl)-methanone (**3d**; $C_{18}H_{14}N_3O$)

Prepared from **1a**; crystallization from EtOH gave pale yellow crystals (69%); m.p.: 294–295°C; IR (KBr): $\bar{\nu} = 3310$, 3228, 3030, 2920, 1635, 1590, 1550, 1530 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 2.29 (s, CH_3), 2.32 (s, CH_3), 2.48 (s, CH_3), 2.75 (s, CH_3), 7.28 (d, $J = 7.8$ Hz, H_{ar}), 7.64–7.70 (m, $3H_{ar}$), 8.32 (s, $1H_{ar}$), 9.30 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 200 MHz): 27.38 (CH_3), 29.43 (CH_3), 29.63 (CH_3), 31.44 (CH_3), 126.61, 129.89, 135.40, 138.34, 138.97, 141.39, 143.08, 143.36, 145.80, 146.38, 149.22, 151.30, 157.02 (aryl), 204.61 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-(2,4-dimethylphenyl)-methanone (**3e**; $C_{18}H_{14}N_3O$)

Prepared from **1a**; crystallization from EtOH gave yellow crystals (77%); m.p.: 264°C; IR (KBr): $\bar{\nu} = 3563$ br, 3380, 3030, 1637, 1600, 1570, 1520, 1416 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 2.05 (s, CH_3), 2.31 (s, CH_3), 2.48 (s, CH_3), 2.63 (s, CH_3), 7.07 (s, $3H_{ar}$), 7.69 (s, $1H_{ar}$), 8.31 (s, $1H_{ar}$), 11.30 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 27.10 (CH_3), 29.32 (CH_3), 30.76 (CH_3), 31.38 (CH_3), 126.77, 130.01, 135.96, 137.33, 140.37, 140.62, 142.67, 143.89, 146.76, 146.22, 147.40, 147.86, 148.99, 158.29 (aryl), 188.16 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-(2,5-dimethylphenyl)-methanone (**3f**; $C_{18}H_{14}N_3O$)

Prepared from **1a**; crystallization from EtOH gave pale yellowish white crystals (82%); m.p.: 287°C; IR (KBr): $\bar{\nu} = 3563$ br, 3380, 3030, 1637, 1600, 1570, 1520, 1416 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 2.05 (s, CH_3), 2.29 (s, CH_3), 2.48 (s, CH_3), 2.66 (s, CH_3), 7.06 (s, $1H_{ar}$), 7.15 (s, $2H_{ar}$), 7.67 (s, $1H_{ar}$), 8.30 (s, $1H_{ar}$), 11.35 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 27.15 (CH_3), 28.88 (CH_3), 30.48 (CH_3), 31.42 (CH_3), 126.60, 129.78, 135.43, 137.64, 138.85, 139.71, 140.78, 142.80, 144.39, 146.14, 148.74, 150.59, 157.28 (aryl), 188.54 (C=O) ppm.

(4-Amino-6,8-dimethylcinnolin-3-yl)-(2,4,6-trimethylphenyl)-methanone (**3g**; $C_{19}H_{16}N_3O$)

Prepared from **1a**; crystallization from ethyl acetate gave pale brown crystals (75%); m.p.: 292°C; IR (KBr): $\bar{\nu} = 3563$ br, 3380, 3030, 1637, 1600, 1570, 1520, 1416 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.11 (s, $2CH_3$), 2.30 (s, CH_3), 2.56 (s, CH_3), 2.87 (s, CH_3), 6.88 (s, $2H_{ar}$), 7.26 (s, NH), 7.45 (s, $1H_{ar}$), 7.57 (s, $1H_{ar}$), 9.78 (br, NH) ppm; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 1.98 (s, $2CH_3$), 2.27 (s, CH_3), 2.47 (s, CH_3), 2.71 (s, CH_3), 6.86 (s, $2H_{ar}$), 7.46 (s, $1H_{ar}$), 8.06 (s, $1H_{ar}$), 8.20 (br, NH), 10.51 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 27.38 (CH_3), 29.47 ($2CH_3$), 30.65 (CH_3), 31.51 (CH_3), 125.78, 128.78, 137.44, 143.15, 143.35, 146.03, 146.29, 147.60, 149.74, 153.31, 154.78 (aryl), 190.32 (C=O) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-phenyl-methanone (**3h**; $C_{17}H_{15}N_3O$)

Prepared from **1h**; crystallization from ethyl acetate gave yellow crystals (36%); m.p.: 160°C, IR (KBr): $\bar{\nu} = 3336$ br, 3126, 2974, 1635, 1610, 1565, 1525, 1473 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 2.91 (s, CH_3), 2.96 (s, CH_3), 5.86 (br, NH_2), 7.34–7.48 (m, $4H_{ar}$), 7.57 (d, $J = 7.6$ Hz, $2H_{ar}$), 7.94 (d, $J = 7.6$ Hz, $1H_{ar}$) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-p-tolyl-methanone (**3i**; $C_{18}H_{17}N_3O$)

Prepared from **1h**; crystallization from diethyl ether gave yellow crystals (83%); m.p.: 152–154°C; IR (KBr): $\bar{\nu} = 3337$ br, 3251, 3130, 2973, 1632, 1574, 1530, 1425, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.44 (s, CH_3), 2.93 (s, CH_3), 3.00 (s, CH_3), 7.30 (m, $3H_{ar}$), 7.54 (d, $J = 7.29$ Hz, $1H_{ar}$), 7.92 (d, $J = 8.0$ Hz, $2H_{ar}$), 8.20 (br, NH_2) ppm; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 2.39 (s, CH_3), 2.75 (s, CH_3), 2.88 (s, CH_3), 7.28 (d, $J = 8.0$ Hz, $2H_{ar}$), 7.36 (d, $J = 7.0$ Hz, $1H_{ar}$), 7.59 (d, $J = 7.0$ Hz, $1H_{ar}$), 7.72 (d, $J = 8.0$ Hz, $2H_{ar}$), 8.50 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 27.95 (CH_3), 31.16 (CH_3), 33.30 (CH_3), 125.32, 128.19, 140.63, 141.24, 142.60, 143.06, 144.76, 146.70, 151.51, 157.12, 157.40 (aryl), 206.55 (C=O) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-(4-ethylphenyl)-methanone (**3j**; $C_{18}H_{17}N_3O$)

Prepared from **1h**; crystallization from MeOH gave faint yellow crystals (70%); m.p.: 195°C; IR (KBr): $\bar{\nu} = 3347$, 3284, 3126, 2932, 1632, 1606, 1555, 1527, 1473 cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 1.25 (t, $J = 7.6$ Hz, CH_3), 2.67 (q, $J = 7.6$ Hz, CH_2), 2.73 (s, CH_3), 2.84 (s, CH_3), 7.36 (m, $3H_{ar}$), 7.60 (d, $J = 7.2$ Hz, $1H_{ar}$), 7.83 (d, $J = 8.0$ Hz, $2H_{ar}$), 9.22 (br, NH_2) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-(3,4-dimethylphenyl)-methanone (**3k**; $C_{18}H_{14}N_3O$)

Prepared from **1h**; crystallization from $CHCl_3$ gave red crystals (59%); m.p.: 225°C; IR (KBr): $\bar{\nu} = 3337$, 3262, 3028, 2971, 1634, 1607, 1566, 1529, 1475 cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 2.29 (s, CH_3), 2.32 (s, CH_3), 2.44 (s, CH_3), 2.48 (s, CH_3), 6.94 (d, $J = 8.0$ Hz, $1H_{ar}$), 7.12 (d, $J = 7.5$ Hz, $1H_{ar}$), 7.57 (s, $1H_{ar}$), 7.64 (s, $2H_{ar}$), 10.00 (br, NH_2) ppm; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.28 (s, $2CH_3$), 2.85–2.87 (d, $2CH_3$), 7.17 (d, $2H_{ar}$), 7.44 (d, $1H_{ar}$), 7.72 (s, $2H_{ar}$), 11.3 (br, NH) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-(2,4-dimethylphenyl)-methanone (**3l**; $C_{18}H_{14}N_3O$)

Prepared from **1h**; crystallization from EtOH gave orange yellow crystals (60%); m.p.: 218–219°C; IR (KBr): $\bar{\nu} = 3461$ br, 3383, 3031, 1635, 1606, 1571, 1527, 1416 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.37 (s, CH_3), 2.39 (s, CH_3), 2.45 (s, CH_3), 2.57 (s, CH_3), 7.12–7.16 (m, $3H_{ar}$), 7.30–7.38 (m, $2H_{ar}$), 11.27 (br, NH) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-(2,5-dimethylphenyl)-methanone (**3m**; $C_{18}H_{14}N_3O$)

Prepared from **1h**; crystallization from MeOH gave orange crystals (55%); m.p.: 235°C; IR (KBr): $\bar{\nu} = 3422$, 3385, 3027, 1638, 1607, 1573, 1526, 1476 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.25 (s, CH_3), 2.32 (s, CH_3), 2.86 (s, CH_3), 2.95 (s, CH_3), 7.11 (s, $2H_{ar}$), 7.17 (s, $1H_{ar}$), 7.23 (d, $J = 7.3$ Hz, $1H_{ar}$), 7.51 (d, $J = 7.3$ Hz, $1H_{ar}$), 11.30 (br, NH) ppm.

(4-Amino-5,8-dimethylcinnolin-3-yl)-(2,4,6-trimethylphenyl)-methanone (**3n**; $C_{19}H_{16}N_3O$)

Prepared from **1h**; crystallization from acetone gave orange crystals (72%); m.p.: 314°C; IR (KBr): $\bar{\nu} = 3553$ br, 3377, 3031, 1637, 1610, 1568, 1525, 1422 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.11 (s, $2CH_3$), 2.30 (s, CH_3), 2.56 (s, CH_3), 2.87 (s, CH_3), 6.88 (s, $2H_{ar}$), 7.45 (s, $1H_{ar}$), 7.57 (s, $1H_{ar}$), 9.78 (br, NH) ppm; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 1.98 (s, $2CH_3$), 2.27 (s, CH_3), 2.47 (s, CH_3), 2.71 (s, CH_3), 6.86 (s, $2H_{ar}$), 7.46 (s, $1H_{ar}$), 8.06 (s, $1H_{ar}$), 8.20 (br, NH), 10.51 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6 δ, 50 MHz): 27.38 (CH_3), 29.47 ($2CH_3$), 30.65 (CH_3), 31.51 (CH_3), 125.78, 128.78, 137.44, 143.15, 143.35, 146.03, 146.29, 147.60, 149.74, 153.31, 154.78 (aryl), 190.32 (C=O) ppm.

(4-Amino-7,8-dimethylcinnolin-3-yl)-p-tolyl-methanone (**3o**; $C_{18}H_{17}N_3O$)

Prepared from **1o**; crystallization from MeOH gave buff crystals (80%); m.p.: 270°C; IR (KBr): $\bar{\nu} = 3345$, 3284, 3127, 2971, 1633, 1567, 1526, 1474, 1385 cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 2.41 (s, CH_3), 2.48 (s, CH_3), 2.70 (s, CH_3), 7.33 (d, $J = 8.0$ Hz, $2H_{ar}$), 7.64 (d, $J = 8.6$ Hz, $1H_{ar}$), 7.82 (d, $J = 8.0$ Hz, $2H_{ar}$), 8.41 (d, $J = 8.6$ Hz, H_{ar}), 9.47 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 13.40 (CH_3), 20.78 (CH_3), 21.64 (CH_3), 115.37, 120.88, 128.93, 130.61, 131.14, 132.16, 133.07, 135.69, 142.28, 143.06, 143.84, 148.25 (aryl), 194.39 (C=O) ppm.

(4-Amino-6-bromo-7-methylcinnolin-3-yl)-(2,5-dimethylphenyl)-methanone (**3p**; $C_{18}H_{17}BrN_3O$)

Prepared from **1q**; crystallization from MeOH gave yellow crystals (32%); m.p.: 297°C; IR (KBr): $\bar{\nu} = 3445$, 3259, 3125, 2965, 1637, 1612, 1587, 1526, 1431, 1387 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.28 (s, CH_3), 2.33 (s, CH_3), 2.67 (s, CH_3), 7.16 (s, $2H_{ar}$), 7.23 (s, $1H_{ar}$), 8.20 (s, $1H_{ar}$), 8.26 (s, $1H_{ar}$), 10.49–11.00 (br, NH_2) ppm; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 2.12 (s, CH_3), 2.29 (s, CH_3), 2.58 (s, CH_3), 7.11 (s, $1H_{ar}$), 7.18 (s, $2H_{ar}$), 8.21 (s, $1H_{ar}$), 8.95 (s, $1H_{ar}$), 9.50 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 29.06 (CH_3), 30.48 (CH_3), 32.94 (CH_3), 125.43, 136.35, 138.24, 139.71, 139.91, 141.63, 143.27, 143.89, 150.83, 152.79, 154.22, 156.49 (aryl), 210.64 (C=O) ppm.

(4-Amino-6-bromo-5-methylcinnolin-3-yl)-2,5-dimethylphenyl-methanone (**3q**; $C_{18}H_{17}BrN_3O$)

Prepared from **1q**; crystallization from EtOH gave pale yellowish white crystals (24%); m.p.: 288°C; IR (KBr): $\bar{\nu} = 3371$ br, 3277, 3130, 2970, 1635, 1610, 1582, 1526, 1431, 1387 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.17 (s, CH_3), 2.20 (s, CH_3), 2.57 (s, CH_3), 7.00 (s, $2H_{ar}$), 7.06 (s, $1H_{ar}$), 7.59 (d, $J = 8.4$ Hz, $1H_{ar}$), 8.93 (d, $J = 8.4$ Hz, $1H_{ar}$), 10.13 (br, NH_2) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 29.32 (CH_3), 30.36 (CH_3), 31.86 (CH_3), 125.11, 130.49, 133.99, 135.44, 139.21, 140.28, 141.05, 142.09, 143.06, 144.10, 146.94, 150.86, 157.36, 159.02 (aryl), 208.51 (C=O) ppm.

2-Amino-7,9-dimethyl-4-phenyl-pyrido[3,2-c]cinnoline-3-nitrile (**4**; $C_{20}H_{15}N_5$)

A mixture of 0.28 g **3a** (1 mmol), 0.07 g malononitrile (1 mmol), and 15 cm^3 pyridine was refluxed for 6 h. Excess pyridine was removed under reduced pressure, and the residue was poured on crushed ice and HCl under vigorous stirring. The solid obtained was washed with H_2O and crystallized from EtOH to give pale yellow crystals (75%).

M.p.: >300°C; IR (KBr): $\bar{\nu} = 3422$, 3345, 2926, 2218, 1617, 1554, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.70 (s, CH_3), 3.06 (s, CH_3), 5.71 (br, NH_2), 7.52–7.57 (m, $5H_{ar}$), 7.65 (s, $1H_{ar}$), 8.34 (s, $1H_{ar}$) ppm.

1,2-Dihydro-7,9-dimethyl-3-(ethylcarboxylate)-4-phenyl-2-oxo-pyrido[3,2-c]cinnoline (**5**; $C_{22}H_{19}N_3O_3$)

A mixture of 0.28 g **3a** (1 mmol) and 10 cm^3 diethyl malonate was heated at 225°C for 3 h. Excess reagent was removed by distillation under reduced pressure, and the residue was washed with diethyl ether and crystallized from toluene to give pale yellow crystals (55%).

M.p.: 220°C; IR (KBr): $\bar{\nu} = 3320$, 3085, 2927, 1723, 1655, 1582, 1489 cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 1.23 (t, $J = 7.5$ Hz, CH_3), 2.70 (s, CH_3), 3.06 (s, CH_3), 4.40 (AB system, $J = 7.5$ Hz, OCH_2), 7.52–7.57 (m, $5H_{ar}$), 7.65 (s, $1H_{ar}$), 8.34 (s, $1H_{ar}$), 12.94 (br, NH), ppm.

7,9-Dimethyl-4-phenyl-3-ethoxypyrido[3,2-c]cinnoline (**6**; $C_{21}H_{20}N_3O$)

A mixture of 0.28 g **3a** (1 mmol) and 15 cm^3 triethyl orthoacetate was heated at 170°C for 7 h. Excess reagent was removed under reduced pressure, and the oily residue was dissolved in 15 cm^3 dry *DMF*.

0.14 g K_2CO_3 were added, and the mixture was heated for 2 h. After concentration, the residue was treated with 20 cm^3 H_2O. The precipitated solid was collected, washed with H_2O, and crystallized from toluene to give white crystals (62%).

M.p.: 293°C; IR (KBr): $\bar{\nu} = 3092$, 2937, 1612, 1562, 1491 cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 1.21 (t, $J = 7.5$ Hz, CH_3), 2.70 (s, CH_3), 3.06 (s, CH_3), 4.54 (q, $J = 7.5$ Hz, OCH_2), 7.20 (s, $1H_{ar}$), 7.52–7.57 (m, $5H_{ar}$), 7.65 (s, $1H_{ar}$), 8.34 (s, $1H_{ar}$) ppm.

7,9-Dimethyl-4-phenyl-2-dimethylaminopyrido[3,2-c]cinnoline (**7**; $C_{21}H_{21}N_4$)

A mixture of 0.28 g **3a** (1 mmol) and 10 cm^3 dimethylacetamide dimethylacetal was heated at 150°C for 3 h. Excess reagent was removed under reduced pressure, and the oily residue was washed with diethyl ether and crystallized from EtOH to give white crystals (72%).

M.p.: 318°C; IR (KBr): $\bar{\nu} = 3092$, 2937, 1612, 1562, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.70 (s, CH_3), 3.06 (s, CH_3), 3.52 (s, $2CH_3$), 7.08 (s, $1H_{ar}$), 7.52–7.57 (m, $5H_{ar}$), 7.65 (s, $1H_{ar}$), 8.34 (s, $1H_{ar}$) ppm.

Acetylation of (4-amino-dimethylcinnolin-3-yl)-aryl-methanones **3a**,**i**; *formation of 4-acetamidocinnolines* **8a**,**b**

A solution of 2.77 g ketones **3a** and **3i** (10 mmol) in 15 cm^3 acetic anhydride was heated to boiling, resulting a dark yellow solution. Within 5 min, needle-shaped crystals began to form. After cooling in ice, the product was filtered off to give **4a**,**b**. The crude products were used for the next step without further purification.

(4-Acetamido-5,8-dimethylcinnolin-3-yl)-phenyl-methanone (**8a**; $C_{21}H_{20}N_3O_2$)

Prepared from **3a**; crystallization from EtOH/H_2O gave grey crystals (85%); m.p.: 172°C; IR (KBr): $\bar{\nu} = 3453$, 3123, 2958, 1710, 1688, 1626, 1579, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.33 (s, $COCH_3$), 2.62 (s, CH_3), 3.09 (s, CH_3), 7.48–7.67 (m, $5H_{ar}$), 7.89 (d, $J = 7.2$ Hz, $2H_{ar}$) ppm.

(4-Acetamido-5,8-dimethylcinnolin-3-yl)-p-tolyl-methanone (**8b**; $C_{22}H_{22}N_3O_2$)

Prepared from **3i**; crystallization from CH_3COOH and H_2O gave brownish red crystals (72%); m.p.: 160°C; IR (KBr): $\bar{\nu} = 3446$, 3130, 2932, 1712, 1690, 1625, 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.08 (s, $COCH_3$), 2.43 (s, CH_3), 2.91 (s, CH_3), 2.97 (s, CH_3), 7.25–7.30 (m, $3H_{ar}$), 7.52 (d, $J = 7.3$ Hz, $1H_{ar}$), 7.91 (d, $J = 8.2$ Hz, $2H_{ar}$) ppm.

Preparation of 1,2-dihydro-4-aryl-2-oxopyrido[3,2-c]cinnolines **9a**,**b**

To a solution of the crude amide **8a** or **8b** (10 mmol) in 25 cm^3 dry *DMF*, 1.4 g K_2CO_3 were added, and the mixture was heated for 2 h. After concentration, the residue was treated with 30 cm^3 H_2O. The *pH* was adjusted to 3–4 by addition of 2 *N* HCl, the precipitated solid was collected, washed with H_2O, and recrystallized from the given solvent to afford **9a**,**b**.

1,2-Dihydro-7,9-dimethyl-4-phenyl-2-oxopyrido[3,2-c]cinnoline (**9a**; $C_{19}H_{15}N_3O$)

Prepared from **8a**; crystallization from *DMF*/H_2O gave white crystals (82%); m.p.: 293°C; IR (KBr): $\bar{\nu} = 3400$, 3144, 3082, 2926, 1656, 1552, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.70 (s, CH_3), 3.06 (s, CH_3), 7.05 (s, $1H_{ar}$), 7.55–7.57 (m, $3H_{ar}$), 7.65 (s, $1H_{ar}$), 7.85–7.87 (m, $2H_{ar}$), 8.34 (s, $1H_{ar}$), 13.50 (br, NH) ppm.

1,2-Dihydro-7,10-dimethyl-4-(p-tolyl)-2-oxopyrido[3,2-c]cinnoline (**9b**; $C_{20}H_{17}N_3O$)

Prepared from **8b**; crystallization from EtOH gave white crystals (47%); m.p.: 202°C; IR (KBr): $\bar{\nu} = 3402, 3083, 2926, 1655, 1554, 1492\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.46 (s, CH_3), 3.03 (s, CH_3), 3.17 (s, CH_3), 6.96 (s, $1H_{ar}$), 7.33 (d, $J = 7.9$ Hz, $2H_{ar}$), 7.57 (d, $J = 7.3$ Hz, $1H_{ar}$), 7.66 (d, $J = 8.0$ Hz, $3H_{ar}$), 11.70 (br, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 20.13 (CH_3), 22.98 (CH_3), 25.75 (CH_3), 115.00, 123.39, 130.65, 130.79, 131.65, 133.39, 134.00, 134.81, 135.66, 135.79, 139.76, 141.13, 149.00, 156.80, (aryl), 163.75 (C=O) ppm.

7,10-Dimethyl-4-phenyl-2-methoxy-pyrido[3,2-c]cinnoline (**10**; $C_{19}H_{17}N_3O$)

A mixture of 0.30 g **8b** (1 mmol), 3 cm^3 KOH (7%), and 0.30 cm^3 CH_3I was stirred overnight at room temperature. The precipitate which separated was washed with diethyl ether and recrystallized from EtOH to give red crystals (36%).

M.p.: > 300°C; IR (KBr): $\bar{\nu} = 3080, 2933, 1682, 1625, 1550, 1492\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 2.43 (s, CH_3), 3.09 (s, CH_3), 3.37 (s, CH_3), 4.24 (s, OCH_3), 7.23 (s, $1H_{ar}$), 7.35 (d, $J = 7.9$ Hz, $2H_{ar}$), 7.62 (m, $2H_{ar}$), 7.76 (d, $J = 7.9$ Hz, $2H_{ar}$) ppm.

References

[1] Amer AM, Attia IAG, El-Mobayad M, Asker S (2000) Polish J Chem **74**: 681
[2] Cignarella G, Barlocco D, Pinna GA, Curzu MM (1994) Acta Chim Slov **41**: 173
[3] Cignarella G, Barlocco D, Pinna GA, Loriga M, Curzu MM, Tofanetti O, Germini M, Cazzulani P, Cavaletti E (1989) J Med Chem **32**: 2277
[4] Lown JW, Morgan AR, Yen SF, Wang YH, Wilson WD (1985) Biochemistry **24**: 4028
[5] Miyamoto K, Matsumoto J, Nakamura S (1990) Jap Patent 02 96 570; Chem Abstr (1990) **113**: 97619
[6] Singerman GM (1973) Chem Heterocycl Compd **27**: 1
[7] Glowka ML, Martynowski D, Napieraj A, Olczak A, Stanczak A, Ochocki Z, Lewgowd W (1999) J Chem Crystallography **29**: 687
[8] Nargund LVG, Nargund KS (1995) Arzneim Forsch **45**: 1131
[9] ICI Americas Inc, JP 61.280.483 (1986) Chem Abstr (1988) **108**: 131839
[10] Stanczak A, Kwapiszewski W, Szadoska A, Pakulska W (1994) Pharmazie **49**: 406 and references therein
[11] Resh JF, EP 328.282 (1989); Chem Abstr (1990) **113**: 120786
[12] Amer AM, El-Bermaui MA, Ahmed AFS, Soliman SM (1999) Monatsh Chem **130**: 1409
[13] Haider H, Heinisch G (1986) Synthesis 862 and references therein
[14] Gewald K, Calderon O, Schaefer H, Hain U (1984) Liebigs Ann Chem **7**: 1390
[15] Spoerri PE, DuBois AS (1949) Organic Reactions, vol V, chapt. 9. Wiley, New York, pp 387–412
[16] Deeb A, El-Mobayad M, Essawy AN, El-Hamid AA, Amer AM (1990) Collect Czech Chem Commun **55**: 728, 2790
[17] El-Mobayad M, Essawy AN, El-Hamid AA, Amer AM (1991) Gazzetta Chimica Italiana **121**: 209
[18] Collins CH (1964) Microbiological methods. Butterworth, London, p 9

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