A Synthesis of Imidazo- and Pyrimido[1,2-*g*][1,6]naphthyridinones

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Arylmethylimidazolines and (3-chlorophenyl)methyl-1,4,5,6-tetrahydropyrimidine amidated 2-chloro-3-pyridinecarbonyl chloride, and potassium *t*-butoxide cyclized the products to linearly fused, tricyclic imidazo-and pyrimido[1,2-*g*][1,6]naphthyridinones. Condensation of ethyl 2-chloro-3-pyridinecarboxylate with 2-(phenylmethyl)imidazoline in the presence of sodium methoxide directly formed the isomeric, angularly fused 8,9-dihydro-6-phenylimidazo[1,2-*a*][1,8]naphthyridin-5(7*H*)-one.

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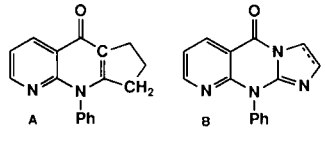
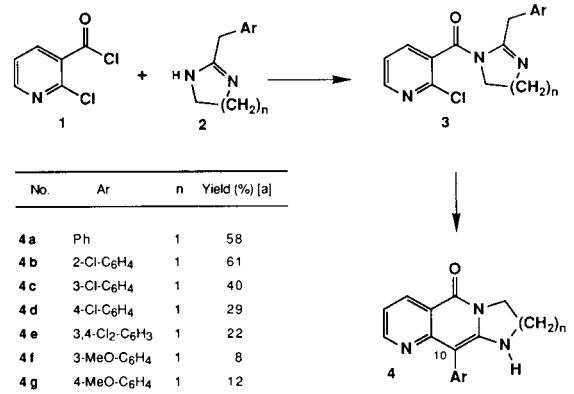
In the course of other work, we found that compounds like **A** [1] and **B** [2,3] possessed similar antiallergy and antiinflammatory activities [1,3]. The activities were exhibited both *in vivo* and *in vitro*. As a consequence, it was of interest to determine whether the structure of the central, fused ring-4-pyridone **A** or 4-pyrimidone **B**-imparted these pharmacological activities. We sought to change this ring, expecting that an important structural change would abolish or augment one or both activities. Here we report a synthesis of the related compounds **4** (Scheme), which contain a 2-pyridone as the central ring. In fact, the *in vivo* and *vitro* activities of pyridones **4** were qualitatively like those common to **A** and **B**, as determined by means of the same assays at comparable doses [4]. The different structures of the (three) central rings so far examined were thus unimportant in determining the common biological activities.



Arylmethylimidazolines **2a-i** and (3-chlorophenyl)methyl-1,4,5,6-tetrahydropyrimidine (**2j**) straightforwardly amidated 2-chloro-3-pyridinecarbonyl chloride, furnishing imidazolides **3** (Scheme). The amidation occurred in dichloromethane solution containing diisopropyl- or triethylamine. In a separate step, potassium *t*-butoxide in hot *t*-butyl alcohol then cyclized intermediates **3** to the desired products **4**. The final step could be carried out with crude, isolated samples of **3**, but isolation was not necessary. When tetrahydrofuran and potassium *t*-butoxide (two equivalents) respectively replaced dichloromethane and the tertiary amine base in the amidation, then compounds **4d** and **4j** formed in a single flask. Whether these changes would, in general, have increased yields was not determined; but treatment with *t*-butoxide in *t*-butyl alcohol furnished neither **4d** nor **4j**.

In some cases, isolation of intermediates **3** by aqueous work-up, or by work-up and subsequent silica gel chromatography, was disadvantageous. Not unexpectedly, compounds **3** proved to be hydrolytically labile. In one instance, column chromatography of **3a**, which survived aqueous work-up, decomposed it to unknown by-products (tlc). Two other by-products were obtained. Compound **5a** was isolated after an aqueous work-up of an amidation. Compound **5b** was isolated after an attempted cyclization of a crude amidation product, which had been given an aqueous work-up. Both compounds **5a** and **5b** evidently arose from hydrolyses of the corresponding intermediates **3i** and **3d**.

Scheme 1

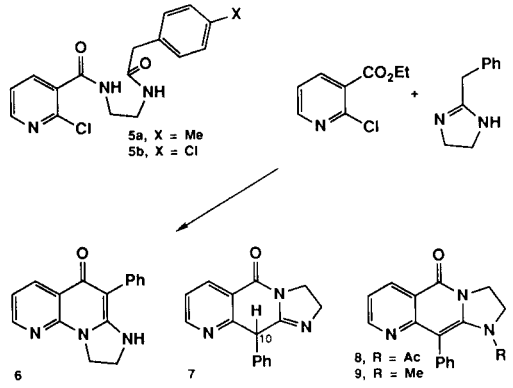


No.	Ar	n	Yield (%) [a]
4a	Ph	1	58
4b	2-Cl-C_6H_4	1	61
4c	3-Cl-C_6H_4	1	40
4d	4-Cl-C_6H_4	1	29
4e	3,4-Cl_2-C_6H_3	1	22
4f	3-MeO-C_6H_4	1	8
4g	4-MeO-C_6H_4	1	12
4h	1-naphthyl	1	39
4i	4-Me-C_6H_4	1	3
4j	3-Cl-C_6H_4	2	10

[a] Yields and conditions are unmaximized and unoptimized, resp.; yields are referred to compounds **2**.

Assignment of the linearly fused ring structures of **4** followed from the method of synthesis, *viz.* amidation of an acid chloride **1** at relatively low temperatures (0-25°). Although imidazoline **2a** condensed with ethyl 2-chloro-3-pyridinecarboxylate in boiling toluene, the product was not **4a** but instead was the angularly fused, isomeric imidazonaphthyridinone **6**. Comparison of uv, mass, and ^1H and ^{13}C nmr spectra, as well as of melting points and R_f-values, established that **4a** differed from **6**. Comparisons of carbonyl δ-values showed which was which. Respectively, the amide-like carbonyl resonances of **4a** and **B** fell at δ 159 and 157 ppm, but the enaminone-like carbonyl carbons of **6** and **A** resonated at lower fields: δ 173 and 174 ppm. The central ring of **4a** contained an enamine-like double bond, of which the phenyl-substituted carbon

(*C*(10)) resonated at a relatively high field (δ 92 ppm). The ir and ^{1}H nmr spectra of **4a**, which included an NH absorption and an exchangeable one-proton N*H* resonance, confirmed the presence of a double bond in the central ring. Any of these last three signals would have been inconsistent with those expected of the isomeric **7**, which was not isolated. Isomer **7**, which lacks an NH group altogether, possesses a C(10) methine hydrogen instead. No methine proton resonance was apparent in the ^{1}H nmr spectrum of **4a**. These data did not exclude yet other tautomers of **4a**, however.



Incidentally, the chemical shifts of the γ pyridine protons of compounds **4** were deshielded by +0.49 ±0.04 ppm from the corresponding *H*(γ) resonance (δ 7.79 ppm) of pyridine in DMSO-d_6. This anisotropic dehielding was useful because it diagnosed cyclizations of **3** to **4**. The corresponding H (γ) resonance (δ 7.98 ppm) in intermediate **3b** (*e.g.*) was not deshielded as much as that in products **4**.

Barium permanganate in refluxing dichloromethane failed to oxidize the methylene groups of compounds **8** and **9**. The latter, *e.g.*, was recovered after about 50 hours and no product could be detected (tlc). The same reagent and similar conditions did aromatize compound **B**, however [3]. Like **B**, compound **4a** reacted, but formed an intractable mixture of several products. A successful aromatization might have formed biologically active products.

EXPERIMENTAL

The ir spectra were determined as potassium bromide pellets unless otherwise stated, and ν-values are in cm^{-1}. These spectra were recorded with Sargent-Welch 3-200, Nicolet Model MX-1 FT-IR, or Perkin-Elmer 727B instruments. The uv spectra were recorded with ethanol solutions unless otherwise noted; λ-values are in nm, and parenthetical ε-values are logarithmic. The uv spectra were determined with a Beckman Model 25 or a Cary Model 118 spectrophotometer. Unless otherwise noted, ^{1}H nmr spectra were determined with perdeuteriodimethyl sulfoxide solutions. The nmr spectra are reported as δ-values in ppm downfield from tetramethylsilane; *J*-values are in Hz. The ^{1}H and ^{13}C nmr spectra were recorded on Varian instruments (FT-80A, EM-390, VXR-200, or XL-200). Electron-impact mass spectra are reported unless specified otherwise; parenthetical numbers immediately following m/z values are relative ion intensities (%). Medium-resolution mass spectra were determined with AES MS-9 or Varian CH5 instruments; high-resolution spectra were recorded with a Varian double-focusing MAT-312 spectrometer operated at 70 eV.

E. Merck (Darmstadt) supplied F-254 silica gel plates for tlc; developed plates were visualized in uv light or in iodine vapor. Baker or Merck provided silica gel for column chromatography, which was done with 60-200 mesh (gravity flow) or 40 μm (nitrogen pressure) particles.

Uncorrected melting points are reported, and were recorded by means of a Thomas-Hoover unimelt apparatus with open capillaries or a Thomas hot-stage apparatus (Model 40). Organic solutions were routinely dried over sodium or magnesium sulfate.

Chemo Dynamics, Inc., supplied 2-chloro-3-pyridinecarbonyl chloride (**1**). The Aldrich Chemical Co. provided 2-(phenylmethyl)imidazoline hydrochloride (**2a**) and 2-(1-naphthylmethyl)-2-imidazoline (**2h**). Other substituted imidazolines used in this work – (2-chlorophenyl)methyl- (**2b**) [5], (3-chlorophenyl)methyl- (**2c**) [5], (4-chlorophenyl)methyl- (**2d**) [5], (3,4-dichlorophenyl)-methyl- (**2e**) [6], (3-methoxyphenyl)methyl- (**2f**) [7], (4-methoxyphenyl)methyl- (**2g**) [8], and 2-(4-methylphenyl)methylimidazoline (**2i**) [9] – are also known compounds, and were prepared by a general method [10] from commercially available phenylacetonitriles. Hydrochloride salts of imidazolines were converted to the corresponding free bases by a standard method. 2-(3-chlorophenylmethyl)-1,4,5,6-tetrahydropyrimidine (**2j**) [5] was prepared similarly [10].

General Method for Amidation of **1** by **2** Yielding **3**.

Solutions (1-1.4 *M*) of acid chloride **1** (1.3-1 equivalents) in dichloromethane were added to stirred, cooled (ice bath) solutions of imidazolines **2** (1 equivalent) and diisopropylethylamine (1.7-2.8 *M*) in dichloromethane. Imidazolines were used as free bases except for **2a**, **2e**, **2f** and **2h**; which were taken as hydrochlorides and treated with enough tertiary amine base to liberate the free imidazoline bases. Triethylamine was used instead of diisopropylethylamine in the cases of **3h** and **3i**. The reactions were allowed to proceed overnight, and ice in the baths was not replenished. The reaction mixtures were washed with water, 1*M* sodium bicarbonate or carbonate solution, and with water. The dried and filtered organic layers were concentrated. The crude amidation products were used directly in the next step; samples of **3b** and **3h** were characterized.

2-(2-Chlorophenyl)methyl)-1-[(2-chloro-3-pyridinyl)carbonyl]-4,5-dihydro-1*H*-imidazole (**3b**).

After crystallization from ethyl acetate, this compound, mp 128.5-130°, was isolated in a yield of 65% from **2b**; ir: 1670 (CO), 1650; ^{1}H nmr: 8.47 (dd, $J(\alpha\text{-}\gamma)$ = 2, $J(\alpha\text{-}\beta)$ = 5, 1H, *H*(α)), 7.98 (dd, $J(\gamma\text{-}\alpha)$ = 2, $J(\gamma\text{-}\beta)$ = 8, 1H, *H*(γ)), 7.48 (dd, $J(\beta\text{-}\gamma)$ = 8, $J(\beta\text{-}\alpha)$ = 5, 1H, *H*(β)), 7.26 (br s, 4H, *Ar*), 3.68 (s, 4H, $-(CH_2)_2-$); ms: 300 (32, [M - Cl]$^+$), 298 (100, [M - Cl]$^+$), 142 (27), 140 (82), 125 (23), 112 (84).

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O$: C, 57.50; H, 3.92; Cl, 21.22; N, 12.57. Found: C, 57.21; H, 3.87; Cl, 20.67; N, 12.37. No acceptable microanalysis for Cl was obtained.

1-[(2-Chloro-3-pyridinyl)carbonyl]-4,5-dihydro-2-(1-naphthalenylmethyl)-1*H*-imidazole (**3h**).

A sample of the crude amidation product crystallized from

methanol giving pure **3h**, mp 148-151°; ir (potassium bromide): 1670 (CO); uv (methanol): 291 (3.43), 280 (3.62), 268 (3.72), 259 (3.71), 222 (4.75); ^{1}H nmr (deuteriochloroform): 8.27 (dd, $J(\alpha$-$\beta)$ = 5, $J(\alpha$-$\gamma)$ = 2, 1H, $H(\alpha)$), 8.00-7.61 (m, 3H, $H(\gamma)$, $H(5)$ and $H(8)$), 7.55-7.19 (m, 5H, $H(2)$, $H(3)$, $H(4)$, $H(6)$ and $H(7)$), 7.00 (dd, $J(\beta$-$\alpha)$ = 5, $J(\beta$-$\gamma)$ = 8, 1H, $H(\beta)$), 4.45 (s, 2H, $ArCH_2$-), 3.87 (s, 4H, 2 -CH_2-); ms: 352 (5, $[M + 1]^+$ for ^{37}Cl), 351 (27, M^+ for ^{37}Cl), 350 (49, $[M - 1]^+$ for ^{37}Cl and $[M + 1]^+$ for ^{35}Cl), 349 (78, M^+ for ^{35}Cl), 348 (100, $[M - 1]^+$ for ^{35}Cl), 314 (60, $[M - Cl]^+$), 210 (3, $[C_9H_7{}^{37}ClN_3O]^+$), 209 (15, $[C_{14}H_{13}N_2]^+$), 208 (10, $[C_9H_7{}^{35}ClN_3O]^+$), 142 (27, $[C_6H_3{}^{37}ClNO]^+$), 141 (28, $[C_{11}H_9]^+$), 140 (82, $[C_6H_3{}^{35}ClNO]^+$), 127 (3, $[C_{10}H_7]^+$), 114 (10, $[C_5H_3{}^{37}ClN]^+$), 112 (31, $[C_5H_3{}^{35}ClN]^+$).

Anal. Calcd. for $C_{20}H_{16}ClN_3O$: C, 68.67; H, 4.61; Cl, 10.14; N, 12.01. Found: C, 68.50; H, 4.66; Cl, 10.32; N, 12.04.

General Method for Cyclizations of **3** to **4**.

Potassium *t*-butoxide (0.7-1.2 mmoles per mmole of imidazoline taken) was added to solutions (0.3-0.8 *M*) of the crude amidation products **2** in *t*-butyl alcohol. Under nitrogen, the resulting reaction mixtures were refluxed 4-8 hours (27 hours in the case of **4h**), cooled, and concentrated. The residues were partitioned between chloroform and water, and combined chloroform solutions were dried, filtered and concentrated. The crude products were then purified as individually described below.

Compounds **4d** and **4i** were made by a modification of this procedure and are separately described.

2,3-Dihydro-10-phenylimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4a**).

Made from 2-(phenylmethyl)imidazoline hydrochloride (**2a**) (23.5 mmoles), crude **4a** solidified on trituration with ethyl acetate. The collected solid (0.418 g, pure by tlc) crystallized from methanol to give **4a**, mp 250-253° dec; ir: 3340 (NH), 1650 (CO), 1620, 1590; uv: 242 sh (4.07), 317 (4.30), 385 (4.55); ^{1}H nmr: 8.56 (dd, $J(8\text{-}7)$ = 4.4, $J(8\text{-}6)$ = 1.9, 1H, $H(8)$), 8.32 (dd, $J(6\text{-}7)$ = 8.1, $J(6\text{-}8)$ = 1.9, 1H, $H(6)$), 7.43 (s, C_6H_5), 7.05 (dd, $J(7\text{-}8)$ = 4.4, $J(7\text{-}6)$ = 8.1, 1H, H)7)), 6.84 (s, 1H, ex., NH), 4.21 (br t, J = 8.1, 2H, -CH_2-), 3.61 (br t, J = 8.1, 2H, -CH_2-); ^{13}C nmr (DMSO-d_6): 159 (C(5)), 154.5 (C(9a)), 153.6 (C(8)), 149 (C(10a)), 134.7 (C(6)), 134.6, (C(1')), 116 (C(7)), 114 (C(5a)), 92 (C(10)), 44 (C(3)*), 42 (C(2)*); ms: 263 (70, M^+), 262 (100, $[M - 1]^+$), 191 (22), 91 (13, $[C_7H_7]^+$).

Assignments of ^{13}C resonances were based partly on an Attached Proton Test [11].

10-(2-Chlorophenyl)-2,3-dihydroimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4b**).

Made from 2-(2-chlorophenyl)methyl)imidazoline (**2b**) (22.1 mmoles), crude **4b** crystallized from methanol giving an analytical sample, mp 295-297° dec; ir: 3330 (NH), 1650 (CO), 1620, 1600, 1590; uv: 242 sh (4.10), 313 (4.33), 380 (3.55); ^{1}H nmr: 8.42 (dd, $J(8\text{-}7)$ = 4, $J(8\text{-}6)$ = 2, 1H, $H(8)$), 8.21 (dd, $J(6\text{-}7)$ = 8, $J(6\text{-}8)$ = 2, 1H, $H(6)$), 7.58-7.12 (m, 4H, Ar), 6.95 (dd, $J(7\text{-}8)$ = 4, $J(7\text{-}6)$ = 8, 1H, $H(7)$), 6.76 (s, 1H, ex., NH), 4.16 (br t, J = 7, 2H, -CH_2-), 3.56 (br t, J = 7, 2H, -CH_2-); ms: 299 (10, M^+ for ^{37}Cl), 297 (30, M^+ for ^{35}Cl), 263 (47), 262 (100, $[M - Cl]^+$), 192 (17), 191 (70).

10-(3-Chlorophenyl)-2,3-dihydroimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4c**).

Compound **4c** was made *via* **3c** from 3-(chlorophenyl)methylimidazoline (**2c**) (100 mmoles). After treatment of **3c** with potassium *t*-butoxide, a precipitate (10.6 g) formed during partitioning between chloroform and water, and the precipitate was collected and reserved. Combined chloroform solutions were dried and filtered; solvent was evaporated to give a dark oil (16.8 g), which solidified on trituration with 2-propyl acetate. The collected solid (5.07 g) was combined with the 10.6 g sample, and the whole crystallized from dimethylformamide to give **4c** (11.9 g, 40% from **2c**), mp 268-272°; ir (mineral oil): 3370 (NH), 1650 (CO), 1615, 1600, 1580; ^{1}H nmr: 8.59 (dd, $J(8\text{-}7)$ = 4.5, $J(8\text{-}6)$ = 2, 1H, $H(8)$), 8.31 (dd, $J(6\text{-}7)$ = 8, $J(6\text{-}8)$ = 2, 1H, $H(6)$), 7.55-7.30 (m, 4H, Ar), 7.06 (dd (superimposed on a br s, ex., -NH), $J(7\text{-}8)$ = 4.5, $J(7\text{-}6)$ = 8, 1H, $H(7)$), 4.23 (br t, J = 8, 2H, -CH_2), 3.64 (br t, J = 8, 2H, -CH_2-); ms: 300 (5, $[M + 1]^+$ for ^{37}Cl), 299 (31, M^+ for ^{37}Cl), 298 (57, $[M - 1]^+$ for ^{37}Cl and $[M + 1]^+$ for ^{35}Cl), 297 (90, M^+ for ^{35}Cl), 296 (100, $[M - 1]^+$ for ^{35}Cl), 225 (17), 131 (28).

10-(3,4-Chlorophenyl)-2,3-dihydroimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4e**).

Made from 2-(3,4-dichlorophenylmethylimidazoline hydrochloride (**2e**) (47 mmoles), crude **4e** solidified during trituration with 2-propyl acetate. The collected solid crystallized from acetone to give **4e** (3.6 g), mp 223-224°; ir (mineral oil): 3140 (NH), 1660 (CO), 1620; ^{1}H nmr: 8.53 (dd, $J(8\text{-}7)$ = 4, $J(8\text{-}6)$ = 2, 1H, $H(8)$), 8.25 (dd, $J(6\text{-}7)$ = 8, $J(6\text{-}8)$ = 2, 1H, $H(6)$), 7.70-7.47 (m, 2H, $H(5')$ and $H(2')$), 7.34 (dd, $J(6'\text{-}5')$ = 8, $J(6'\text{-}2')$ = 2, 1H, $H(6')$), 7.17 (br s, 1H, NH, ex.), 7.02 (dd, $J(7\text{-}8)$ = 4, $J(7\text{-}6)$ = 8, 1H, $H(7)$), 4.15 (t, J = 8, 2H, -CH_2-), 3.60 (t, J = 8, 2H, -CH_2-)); ms: 336 (2, $[M + 1]^+$ for $^{37}Cl_2$), 335 (13, M^+ for $^{37}Cl_2$), 334 (28, $[M - 1]^+$ for $^{37}Cl_2$ and $[M + 1]^+$ for $^{37}Cl^{35}Cl$), 333 (82, M^+ for $^{35}Cl_2$), 332 (96, $[M - 1]^+$ for $^{37}Cl^{35}Cl$ and $[M + 1]^+$ for $^{35}Cl_2$), 331 (96, M^+ for $^{35}Cl_2$), 330 (100, $[M - 1]^+$ for $^{35}Cl_2$), 148 (23).

2,3-Dihydro-10-(3-methoxyphenyl)imidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4f**).

Made from 2-(3-methoxyphenyl)methylimidazoline hydrochloride (**2f**) (47.0 mmoles), crude **4f** solidified during trituration with ethyl acetate. The collected solid (3.15 g) crystallized from acetonitrile to give **4f** (0.702 g), mp 268-271°; ir (mineral oil): 3350 (NH), 1660 (CO), 1615; ^{1}H nmr 8.53 (dd, $J(8\text{-}7)$ = 4, $J(8\text{-}6)$ = 2, 1H, $H(8)$), 8.26 (dd, $J(6\text{-}7)$ = 8, $J(6\text{-}8)$ = 2, 1H, $H(6)$), 7.40-6.67 (m, 6H, Ar, $H(7)$ and NH)), 4.16 (br t, J = 8, 2H, -CH_2-), 3.75 (s, 3H, -OCH_3), 3.57 (br t, J = 8, 2H, -CH_2-); ms: 294 (42, $[M + 1]^+$), 293 (100, M^+), 292 (100, $[M - 1]^+$), 277 (63), 262 (11, $[M - OMe]^+$).

2,3-Dihydro-10-(4-methoxyphenyl)imidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4g**).

Made from 2-(4-methoxyphenyl)methylimidazoline (**2g**) (21.8 mmoles), crude **4g** was a dark oil (6.28 g), which contained one major and 6-10 minor components (tlc). Chromatography over silica gel and elution with methanol-chloroform (1:99 by volume), followed by crystallization of the fastest running component from methanol, gave **4g** (0.800 g, 12% from **2g**), mp 225.0-227.5°; ir: 3320 (NH), 1650 (CO), 1620, 1580; ^{1}H nmr: 8.54 (dd, $J(8\text{-}7)$ = 4.5, $J(8\text{-}6)$ = 2, 1H, $H(8)$), 8.32 (dd, $J(6\text{-}7)$ = 7.5, $J(6\text{-}8)$ = 2, 1H, $H(6)$), 7.32 (d, J = 9, 2H, Ar), 7.01 (3 lines of a dd, $H(7)$) and 6.98 (d, J = 9, Ar) (total of 3H), 6.80 (br s, 1H, NH), 4.18 (br t, J = 8, 2H, -CH_2-), 3.58 (br t, J = 8, 2H, -CH_2-); ms: 293 (100, M^+), 292 (78, $[M - 1]^+$), 250 (25), 179 (14).

2,3-Dihydro-10-(1-naphthalenyl)imidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4h**).

Made from 2-(1-naphthylmethyl)-2-imidazoline hydrochloride (**2h**) (100 mmoles), crude **4h** was a semi-solid (31.7 g), which solidified on trituration with acetonitrile. The collected solid crystallized from acetonitrile to give **4h** (11.7 g, 39% from **2h**), mp 225-227°; ir: 1660 (CO), 1620, 1585; uv (methanol): 221 (4.89), 244 sh (3.95), 314 (4.07); ^{1}H nmr: 8.38-8.28 (m, 2H, *H*(8) and *H*(8')), 7.99-7.89 (m, 2H, *H*(6), and *H*(5')), 7.62-7.28 (m, 5H, *Ar*), 7.00 (dd, *J* = 5, *J* = 8, 1H, *H*(7)), 6.58 (s, 1H, N*H*), 4.22 (t, *J*(3-2) = 8, 2H, *H*(3)), 3.55 (t, *J*(2-3) = 8, 2H, *H*(2)); ms: 315 (3, [M + 2]$^+$), 314 (22, [M + 1]$^+$), 313 (94, M$^+$), 312 (100, [M - 1]$^+$), 241 (18).

2,3-Dihydro-10-(4-methylphenyl)imidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4i**).

Made from 2-(4-methylphenyl)methyl)imidazoline (**2i**) (144 mmoles), crude **4i** was a brown semi-solid (41.5 g), which contained 6-7 components (tlc). A filtered solution of this material in 2-propyl acetate was concentrated, and the residue (32 g) was chromatographed over silica gel. Elution of the third and fourth fastest running components with alcohol-free chloroform gave a gum (6.7 g) which solidified after trituration with ether. Crystallization of the collected solid from acetonitrile gave **4i** (1.2 g, 3% from **2i**), mp 247-249°; ir: 3220 (NH), 1670 (CO), 1655; uv (ethanol): 250 sh (3.76), 318 (3.99), 390 (3.28); ^{1}H nmr (deuteriochloroform): 8.67 (dd, *J*(8-7) = 5, *J*(8-6) = 2, 1H, *H*(8)), 8.50 (dd, *J*(6-8) = 2, *J*(6-7) = 8, 1H, *H*(6)), 7.40-7.09 (m, 4H, *Ar*), 7.00 (dd, *J*(7-8) = 5, *J*(7-6) = 8, 1H, *H*(7)), 4.60 (s, 1H, ex., N*H*), 4.30 (t, J = 8, 2H, -CH_2-), 3.66 (t, J = 8, 2H, -CH_2-), 2.34 (s, 3H, -CH_3); ms: 279 (4, [M + 2]$^+$), 278 (36, [M + 1]$^+$), 277 (97, M$^+$), 276 (100, [M - 1]$^+$).

10-(4-Chlorophenyl)-2,3-dihydroimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**4d**).

Acid chloride **1** (4.4 g, 25 mmoles) in tetrahydrofuran (55 ml) was added to a stirred, cooled (ice-acetone bath) mixture of imidazoline **2d** (4.9 g, 25 mmoles), potassium *t*-butoxide (2.8 g, 25 mmoles) and tetrahydrofuran (200 ml). The mixture was kept in the bath for 15 minutes, and was then allowed to warm over 15 minutes to 20°. Potassium *t*-butoxide (2.8 g, 25 mmoles) was added; the resulting dark red solution formed a precipitate overnight. Solvent was evaporated, and the residue was partitioned between chloroform and water. The chloroform solution was washed with 1*M* sodium carbonate and with water, and was dried, filtered, and concentrated. Crystallization of the residue from acetonitrile gave **4d** (2.2 g, 29%), mp 260-262°; ir: 3390 (NH), 1660 (CO); ^{1}H nmr (deuteriochloroform): 8.69 (dd, *J*(8-7) = 4, *J*(8-6) = 2, 1H, *H*(8)), 8.53 (dd, *J*(6-7) = 8, *J*(6-8) = 2, 1H, *H*(6)), 7.43 (s, 4H, *Ar*), 7.09 (dd, *J*(7-8) = 4, *J*(7-6) = 8, 1H, *H*(7)), 4.70 (s, N*H*), 4.35 (br t, *J* = 8, -CH_2-), 3.76 (br t, *J* = 8, -CH_2); ms: 300 (6, [M + 1]$^+$ for ^{37}Cl), 299 (36, M$^+$ for ^{37}Cl), 298 (60, [M - 1]$^+$ for ^{37}Cl and [M + 1]$^+$ for ^{35}Cl), 297 (100, M$^+$ for ^{35}Cl), 296 (99, [M - 1]$^+$ for ^{35}Cl), 131 (47).

11-(3-Chlorophenyl)-1,2,3,4-tetrahydro-6*H*-pyrimido[1,2-*g*][1,6]-naphthyridin-6-one (**4j**).

Potassium *t*-butoxide (2.8 g, 25 mmoles) was added to a stirred, cooled (ice-acetone bath) mixture of **2j** (5.2 g, 25 mmoles) and tetrahydrofuran (125 ml). A solution of acid chloride **1** (4.4 g, 25 mmoles) in tetrahydrofuran (55 ml) was then added over 10 minutes. The resulting mixture, which deposited a precipitate, was allowed to stir for 15 minutes at −5 to −10°, and was then allowed to warm to 20° over 30 minutes. A second equivalent of potassium *t*-butoxide (2.8 g, 25 mmoles) was added, and the resulting mixture was allowed to stir at ambient temperature for three days. Solvent was evaporated, and the residue was partitioned between chloroform and water. Combined chloroform solutions were washed with water, 1*M* sodium carbonate solution and with water. The dried, filtered solution was concentrated, and the residue crystallized from ethanol to give **4j** (0.80 g, 10% from **2j**), mp 201-203°; ir (dichloromethane): 3440 (NH), 1655 (CO), 1595; ^{1}H nmr (deuteriochloroform): 8.49 (dd, *J*(9-8) = 4, *J*(9-7) = 2, 1H, *H*(9)), 8.39 (dd, *J*(7-8) = 8, *J*(7-9) = 2, 1H, *H*(7)), 7.50-7.09 (m, 4H, *Ar*), 6.92 (dd, *J*(8-7) = 8, *J*(8-9) = 4, 1H, *H*(8)), 4.65 (br s, 1H, N*H*), 4.13 (t, *J* = 6, 2H, -(CH_2-), 3.29 (m, 2H, -CH_2-), 2.05 (m, 2H, -CH_2-); ms: 314 (6, [M + 1]$^+$ for ^{37}Cl), 313 (34, M$^+$ for ^{37}Cl), 312 (60, [M - 1]$^+$ for ^{37}Cl and [M + 1]$^+$ for ^{35}Cl), 311 (97, M$^+$ for ^{35}Cl), 310 (100, [M - 1]$^+$ for ^{35}Cl), 276 (9, [M - Cl]$^+$), 275 (23, [M - HCl]$^+$), 138 (21), 113 (2), 111 (1).

2-Chloro-*N*-[2-[[4-methylphenyl)acetyl]amino]ethyl]-3-pyridinecarboxamide (**5a**).

Compound **5a** was isolated by filtration during aqueous work-up following treatment of acid chloride **1** with 2-(4-methylphenyl)-methylimidazoline (**2i**). Compound **5a**, mp 178-182°, crystallized from acetonitrile; ir: 3280 (NH), 1650 (CO); uv (ethanol): 208 sh (4.28), 259 (3.49), 266 (3.55), 272 (3.47); ^{1}H nmr: 8.50 (br s, 1H, N*H*), 8.41 (dd, *J*(α-β) = 5, *J*(α-γ) = 2, 1H *H*(α)), 7.96 (br s, 1H, N*H*), 7.78 (dd, *J*(γ-β) = 7.5, *J*(γ-α) = 2, 1H, *H*(γ)), 7.40 (dd, *J*(β-α) = 5, *J*(β-γ) = 7.5, 1H, *H*(β)), 7.10 (s, 4H, *Ar*), 3.43-3.04 (m, 6H, NCH_2CH_2N and ArCH_2CO), 2.26 (s, 3H, CH_3); ^{13}C nmr (perdeuteriodimethyl sulfoxide): 100 MHz 170 (*C*O), 165 (*C*O), 150 (H*C*(α)), 146 (Cl*C*(α)), 138 (*C*(γ)), 135 (CO*C*(β)), 133.1 (*C*(1')*), 133.0 (*C*(4')*), 128.8 (*Ar*), 128.7 (*Ar*), 123 (H*C*(β)), 42 (Ar*C*H$_2$-), 38.9 (N*C*H$_2$-), 38.1 (N*C*H$_2$), 20 (*C*H$_3$); ms: 334 (0.25, [M + 1]$^+$ for ^{37}Cl), 333 (1, M$^+$ for ^{37}Cl), 332 (0.68, [M + 1]$^+$ for ^{35}Cl), 331 (2, M$^+$ for ^{35}Cl), 228 (2, [$C_9H_9{}^{37}ClN_3O_2$]$^+$), 226 (6, [$C_9H_9{}^{35}ClN_3O_2$]$^+$), 149 (6, [$C_9H_{11}NO$]$^+$), 142 (32, [$C_6H_3{}^{37}ClNO$]$^+$), 140 (100, [$C_6H_3{}^{35}ClNO$]$^+$), 114 (8, [$C_6H_3{}^{37}ClN$]$^+$), 112 (24, [$C_6H_3{}^{35}ClN$]$^+$), 105 (95, [C_8H_9]$^+$), 91 (11, [C_7H_7]$^+$).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; Cl, 10.68; N, 12.66. Found: C, 61.38; H, 5.46; Cl, 10.93; N, 12.75.

2-Chloro-*N*-[2-[[4-chlorophenyl)acetyl]amino]ethyl]-3-pyridinecarboxamide (**5b**).

This compound was isolated by filtration during aqueous work-up following preparation of **4d**. Compound **5b**, mp 194-196.5°, crystallized from methanol; ir: 3280 (NH), 1650; ^{1}H nmr: 8.50 (br s, 1H, N*H*), 8.42 (dd, *J*(α,β) = 4, *J*(α-γ) = 2, 1H, *H*(α)), 8.05 (br s, 1H, N*H*), 7.79 (dd, *J*(γ-β) = 8, *J*(γ-α) = 2, 1H, *H*(γ)), 7.42 (dd, *J*(β-α) = 8, *J*(β-α) = 4, 1H, *H*(β)), 7.27 (s, 4H, *Ar*), 3.34-3.12 (m, 6H, NCH_2CH_2N and ArCH_2CO); ^{13}C nmr (perdeuteriodimethyl sulfoxide): 50 MHz 170 (*C*O), 165 (*C*O), 150 (H*C*(α)), 146 (Cl*C*(α)), 138 (*C*(9γ)), 135 (CO*C*(β)), 133 (*C*(1')), 131.0 (*C*(4')), 130.8 (*C*(3')) and *C*(5')), 128 (*C*(2')) and *C*(6')), 123 (H*C*(β)), 42 (Ar*C*H$_2$CO), 39 (*C*H$_2$N), 38 (*C*H$_2$N); ms: 353 (4, M$^+$ for ^{37}Cl^{35}Cl), 352 (7), 351 (M$^+$ for ^{35}Cl$_2$), 228 (6, [$C_9H_9{}^{37}ClN_3O_2$]$^+$), 226 (20, [$C_9H_9{}^{35}ClN_3O_2$]$^+$), 197 (4, [$C_{10}H_{10}{}^{37}ClNO$]$^+$), 195 (9, [$C_{10}H_{10}{}^{37}ClNO$]$^+$), 184 (11, [$C_8H_7{}^{37}ClN_2O$]$^+$), 182 (29, [$C_8H_7{}^{35}ClN_2O$]$^+$), 171 (8, [$C_8H_8{}^{37}ClNO$]$^+$), 169 (18, [$C_8H_8{}^{35}ClNO$]$^+$), 142 (37, [$C_6H_3{}^{37}ClNO$]$^+$), 140 (100, [$C_6H_3{}^{35}ClNO$]$^+$), 127 (20, [$C_7H_6{}^{37}Cl$]$^+$), 125 (61, [$C_7H_6{}^{35}Cl$]$^+$), 114 (9, [$C_5H_3{}^{37}ClN$]$^+$), 112 (31, [$C_5H_3{}^{35}ClN$]$^+$), 106 (46).

Anal. Calcd. for $C_{16}H_{15}Cl_2N_3O_2$: C, 54.56; H, 4.29; Cl, 20.13; N, 11.93. Found: C, 54.54; H, 4.23; Cl, 20.12; N, 11.90.

8,9-Dihydro-6-phenylimidazo[1,2-*a*][1,8]naphthyridin-5(7*H*)-one (**6**).

A solution of 2-(phenylmethyl)imidazoline (**2a**) (13.6 g, 84.9 mmoles) and ethyl 2-chloropyridinecarboxylate (15.7 g, 84.6 mmoles) in toluene (100 ml) was added to sodium methoxide (10.2 g, 189 mmoles) in toluene (60 ml). The reaction mixture was refluxed 17 hours, cooled, and poured into water. Toluene was removed by steam distillation, and the residue was crystallized from acetonitrile to give **6** (6.8 g, 30%). Recrystallization from acetonitrile gave an analytical sample, mp 239-240°; ir (mineral oil): 3340-3100 (NH), 1610, 1520; uv: 244 (4.17), 277 (4.13), 318 (4.06); ^{1}H nmr: 8.6 (dd, *J*(2-3) = 4.5, *J*(2-4) = 1.5, 1H, *H*(2)), 8.37 (dd, *J*(4-3) = 7.5, *J*(4-2) = 1.5, 1H, *H*(4)), 7.67-7.07 (br m, $-C_6H_5$ plus *H*(3)), 7.0-6.5 (br, N*H*), 4.43 (br t, *J* = 7.5, $-CH_2-$), 3.70 (br t, *J* = 7.5, $-CH_2-$); ^{13}C nmr: 173 (*C*(5)), 155 (*C*(9b)), 151 (*C*(2)), 148 (*C*(6a)), 134.6 (*C*(4)), 134.5 (*C*(1')), 119 (*C*(4a)), 118 (*C*(3)), 99 (*C*(6)), 45 (*C*(8)*), 42 (*C*(9)*); ms: 263 (63, M$^+$), 262 (100, [M - 1]$^+$).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.92; H, 4.76; N, 16.24.

1-Acetyl-2,3-dihydro-10-phenylimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**8**).

After 30 hours reflux and standard work-up, compound **4a** (5.50 g, 20.89 mmoles), acetic anhydride (10 ml), and pyridine (60 ml) gave **8**, which was eluted from silica gel with chloroform. Compound **8** (4.40 g, 69%), mp 229-231°, crystallized from chloroform-petroleum ether; ir (dichloromethane): 1670 (CO), 1620 (MeCO), 1600, 1560, 1440; ^{1}H nmr (deuteriochloroform): 8.90 (dd, *J*(8-7) = 4.5, *J*(8-6) = 2, 1H, *H*(8)), 8.70 (dd, *J*(6-7) = 7.5, *J*(6-8) = 2, 1H, *H*(6)), 7.55-7.43 (m, $-C_6H_5$), 7.35 (dd, *J*(7-8) = 4.5, *J*(7-6) = 7.5, 1H, *H* (7)), 4.26 and 4.21 (overlapping t, *J* = 7.5, 4H, $-(CH_2)_2-$), 1.52 (s, 3H, CH_3CO-); ms: 305 (51, M$^+$), 262 (100, [M - MeCO-]$^+$).

2,3-Dihydro-1-methyl-10-phenylimidazo[1,2-*g*][1,6]naphthyridin-5(1*H*)-one (**9**).

Compound **4a** (2.63 g, 10 mmoles) in dry dimethylformamide (100 ml) was added to sodium hydride (0.25 g of 60% mineral oil dispersion, 10.5 mmoles) suspended in dimethylformamide (25 ml) at 25° under nitrogen. The mixture was stirred at 25° for 1 hour. Methyl iodide (8.5 g, 59.9 mmoles) was slowly added, and the resulting mixture was stirred at 25° for 15 hours. The mixture was poured into ice and water (500 g) and the product was extracted with dichloromethane. Combined extracts were washed with water and brine, and were dried, filtered, and concentrated. Crystallization of the residue from chloroform-acetone gave **9** (2.39 g, 87%), mp 237-240°; ir (dichloromethane): 1660 (CO), 1610, 1600, 1460; ^{1}H nmr (deuteriochloroform): 8.65 (dd, *J*(8-7) = 5, *J*(8-6) = 2, 1H, *H*(8)), 8.50 (dd, *J*(6-7) = 7.5, *J*(6-8) = 2, 1H, *H*(6)), 7.45 (s, C_6H_5), 7.00 (dd, *J*(7-8) = 5, *J*(7-6) = 7.5, 1H, *H*(7)), 4.23 (br t, *J* = 7.5, 2H, $-CH_2-$), 3.57 (br t, *J* = 7.5, 2H, $-CH_2-$), 2.39 (s, 3H, $-CH_3$); ms: 278 (19, [M + 1]$^+$), 277 (90, M$^+$), 276 (100, [M - 1]$^+$), 262 (4, [M - Me]$^+$), 260 (27).

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