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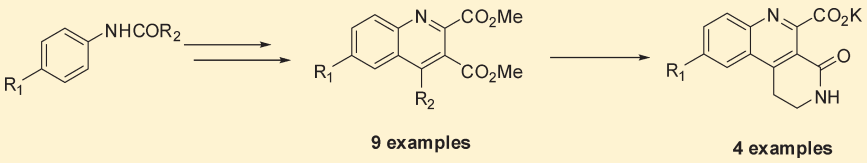
Synthesis of Functionalized Quinolines and Benzo[*c*][2,7]naphthyridines Based on a Photo-Fries Rearrangement

Giacomo Guerrini,[†] Maurizio Taddei,[‡] and Fabio Ponticelli*[,†]

[†]Dipartimento di Chimica and [‡]Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro 2, I-53100 Siena, Italy

Supporting Information

ABSTRACT:



An efficient one-pot method for the synthesis of functionalized quinolines and tetrahydronaphthyridines has been developed. The photo-Fries rearrangement of *p*-substituted anilides afforded differently substituted *o*-amino ketones that reacted in situ with acetylenic Michael acceptors such as dimethyl acetylenedicarboxylate (DMAD) to give 6,4-disubstituted quinoline 2,3-dicarboxylates. Starting from anilides derived from β-alanine, a naphthyridine nucleus can also be assembled.

Quinoline is a common structural motif found in many natural products with remarkable pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used as antimalarial (chloroquine and mefloquine), anti-inflammatory, antiasthmatic, antibacterial, and antihypertensive activities.[1] Benzo[*c*][2,7]-naphthyridine is also a nucleus present in alkaloids isolated from marine organisms with diverse biological activities,[2] such as inhibition of phosphoinositide-dependent protein kinase 1 (PDK-1) involved in the progression of some kinds of cancer, release of calcium, antiviral and antimicrobial activity, and cytotoxicity.[3] A general retrosynthetic approach to quinolines and naphthyridines suggests that aromatic *ortho*-amino ketones are useful building blocks for the preparation of both heterocyclic systems. However, selective access to these types of compounds is troublesome, requiring multistep procedures, harsh reaction conditions, toxic and/or expensive reagents, and tedious protection/deprotection sequences.[4]

Recently, we described a rapid transformation of anilides into aromatic *o*-amino ketones based on the photochemical version of the Fries rearrangement[5] that allowed easy preparation of 1,4-benzodiazepines[6] and quinazolines,[7] two important classes of organic scaffolds. We report here that the same class of aromatic *o*-amino ketones (**II**) can be used for a one-pot two-step procedure that starts from the anilide (**I**) and gives directly quinolines 2,3-dicarboxylate (**III**), easily transformed, through an additional high-yielding step, into benzo[*c*][2,7]-naphthyridines (**IV**) (Figure 1).

In order to investigate the viability of the project, we started to explore the variety of applications in the first step transformation of anilides into aromatic *o*-aminophenones. The Fries reaction largely used for the transformation of esters into substituted

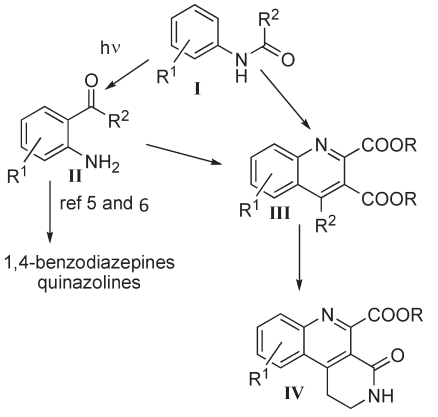


Figure 1. Possible reaction paths of anilides (**I**).

phenols has found less application in its "aza version" as the reaction is generally carried out in the presence of corrosive Lewis acids not compatible with the presence of functional groups. Acetanilide **1a** was employed as the model substrate to investigate the best conditions for the photo-Fries rearrangement. Several experiments were carried out in ethanol and acetonitrile with a multilamps apparatus at 254 and 310 nm. The 254 nm lamp and degassed acetonitrile gave better results in terms of conversion and isolated yields of **2a**. The presence of sensitizer or quencher reagents (i.e., xylene, benzophenone, piperylene, etc.) had no effect of the yield of the photochemical process. The presence of an electron-donating substituent on the

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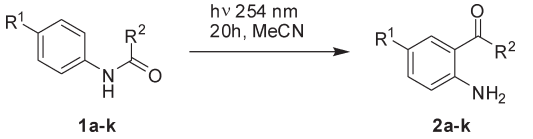
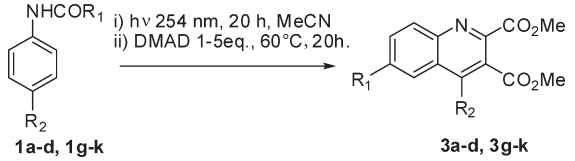
Table 1. Photochemistry of the Aromatic Amides 1a−k[a]



entry	compound	R_1	R_2	product	yield (%)[b]
1	**1a**	H	Me	**2a**	87[c]
2	**1b**	Me	Me	**2b**	56
3	**1c**	OMe	Me	**2c**	71
4	**1d**	F	Me	**2d**	64
5	**1e**	Cl	Me	**2e**	20
6	**1f**	NO_2	Me	**2f**	5
7	**1g**	H	$(CH_2)_2NHCbz$	**2g**	38
8	**1h**	Me	$(CH_2)_2NHCbz$	**2h**	26
9	**1i**	OMe	$(CH_2)_2NHCbz$	**2i**	41
10	**1j**	F	$(CH_2)_2NHCbz$	**2j**	34
11	**1k**	Me	$(CH_2)_3NHCbz$	**2k**	34

[a] Reaction conditions: 0.1 M solution of amides in degassed MeCN, irradiated at 254 nm with a 2 × 15 W low-pressure mercury lamp for 20 h. [b] Calculated yields on NMR spectra. [c] The *ortho* (47%) + *para* (40%) isomers.

Table 2. One-Pot (Two-Step) Preparation of Quinolines 3a−d and 3g−k



entry	compound	equiv of DMAD	product	yield (%)[a]
1	**1a**	1	**3a**	
2	**1b**	1	**3b**	67
3	**1c**	1	**3c**	40
4	**1d**	1	**3d**	61
5	**1g**	5	**3g**	36
6	**1h**	5	**3h**	48
7	**1i**	5	**3i**	38
8	**1j**	5	**3j**	42
9	**1k**	5	**3k**	35

[a] Isolated yields.

aromatic ring gave acceptable yields of the rearranged product (entries 2, 3, 8, 9, and 11 in Table 1), whereas with anilides carrying a nitro group or a chlorine atom (entries 5 and 6 in Table 1), the reaction proceeded with low conversion and poor yields, highlighting the application limits of the reaction. However, a library of *o*-aminophenones was obtained (see Table 1).

When a Michael acceptor such as dimethyl acetylenedicarboxylate (DMAD) was added directly in the solution at the end of the photo-Fries rearrangement, a series of functionalized quinolines 2,3-dicarboxylate (**III**) can be prepared. The results of this one-pot (two-step) procedure are collected in Table 2. The same products can be obtained from a stepwise procedure by rt reaction of aminophenones **2a−d** and **2g−k** with DMAD (yields ranging

Table 3. Yield Comparison between Stepwise and One-Pot Procedures

compound	stepwise procedure yield (%)[a]	one-pot (two-step) procedure yield (%)	yield enhancement (%)
1a	28 (47 + 60)		
1b	32 (56 + 57)	67	+35
1c	36 (71 + 50)	40	+4
1d	44 (64 + 69)	61	+17
1g		36	+36
1h	15 (26 + 56)	48	+33
1i	31 (41 + 76)	38	+7
1j	23 (34 + 68)	42	+19
1k	24 (34 + 72)	35	+11

[a] Single step yields (Fries + Michael) shown in parentheses.

Scheme 1. Proposed Mechanism for the Formation of Quinolines 3a−d and 3g−k

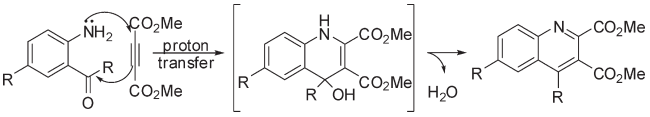
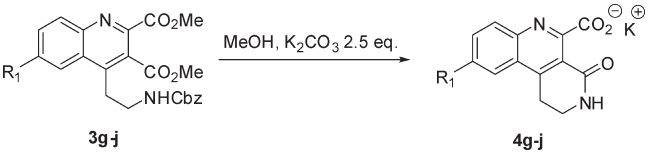


Table 4. Preparation of Naphthyridines 4g−j



compound	yield (%)[a]
3g	70
3h	81
3i	83
3j	74

[a] Isolated yields.

from 58 to 78%). It is interesting to notice that, with respect to the stepwise procedure, in the one-pot (two-step) process, it is possible to obtain an enhancement of the yields (see Table 3).

On the other hand, the use of different olefinic or monosubstituted acetylenes rather than DMAD gave bad results, probably because of the poor nature of Michael acceptors toward the amino group.[8] The Michael mechanism is in accord with what was observed on similar substrates in a recent work.[9]

Formation of quinolines can be accounted for by the mechanism illustrated in Scheme 1.

Starting from the β-Ala derivatives (**1g−k**), it is also possible that the closing of the third heterocyclic ring obtains the 1,2,3,4-tetrahydrobenzo[*c*][2,7]naphthyridine system (**IV**). The reaction was carried out using K_2CO_3 as the base in MeOH at rt with hydrolysis of the methyl ester and removal of the Cbz protection. In these conditions, the potassium salts **4g−k** were isolated in good yields as solid products (Table 4).

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This behavior was strictly related to the ring size as attempts to extend this protocol to the γ-Ala derivative **1k** gave bad results. It is possible that the failure of our effort to close the third heterocycle on the molecule **3k** could be due to the competitive formation of polymeric material.

In conclusion, we have herein reported an innovative and convenient synthetic approach for the synthesis of two important classes of heterocyclic scaffolds using the capability of the aromatic amides to give the photo-Fries rearrangement. Quinolines from simple acetanilides (**1a**−**d**) and β-Ala (**1g**−**j**) or γ-Ala (**1k**) derivatives have been obtained with yields ranging from modest to good using a single one-pot procedure. Good yields have been obtained for the cyclization of ketones **2h**−**k** to functionalized tetrahydronaphthyridines.

EXPERIMENTAL SECTION

General. Melting points were determined with a hot stage apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 27 °C ($CDCl_3$ or CD_3OD), unless otherwise stated, with an instrument operating at 200.13 and 50.33 MHz, respectively, or with an instrument operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are reported in parts per million from internal TMS. Mass spectra were recorded in the positive or negative ion mode with an instrument by using electrospray ionization. HRMS-ESI data were recorded with a Orbitrap instrument. All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (0.040−0.063 mm).

General Procedure for Preparation of Anilides 1a−g. The starting amine was dissolved in anhydrous conditions and under nitrogen atmosphere in dry dichloromethane at 0 °C. Then triethylamine (2.0 equiv) and acetyl chloride (1.4 equiv) were poured into the solution, and the reaction was monitored by TLC (1:1 petroleum ether/AcOEt). The resulting amide was purified by crystallization from water.

Melting points and NMR spectra were identical to those obtained with authentic samples.[10]

General Procedure for Preparation of Anilines 2a−k. A 0.1 M solution of the anilides (**1a**−**k**) (0.5 mmol in 5 mL of MeCN degassed with two cycles of freeze−thaw) was irradiated at 254 nm in a quartz sealed tube using two low-pressure mercury lamps with a total power of 30 W for 20 h at room temperature. After removal of the solvent under reduced pressure, the residues were purified by column chromatography with a variable ratio of petroleum ether/ethyl acetate.

General Procedure for the One-Pot Preparation of Quinolines 3b−d and 3h−k. The 0.1 M solutions in MeCN (degassed with two cycles of freeze−thaw) of the anilides (**1b**−**d** and **1g**−**k**) were irradiated at 254 nm in a quartz sealed tube using a low-pressure mercury lamp for 20 h at room temperature. To the crude reaction mixtures and in the same sealed tube was then added 1−5 equiv of dimethyl acetylenedicarboxylate (DMAD), and the solutions were warmed to 60 °C under magnetic stirring overnight. After removal of the solvent under reduced pressure, the residues were purified by column chromatography with a variable ratio of petroleum ether/ethyl acetate. Compound **3a** has been obtained with the stepwise procedure only.

1-(2-Amino-5-methylphenyl)ethanone, 2b: 41 mg, 56%; chromatographic eluent, petroleum ether/AcOEt 2:1. Melting point and NMR spectra were identical to those obtained with an authentic sample.[11]

1-(2-Amino-5-methoxyphenyl)ethanone, 2c: 58 mg, 71%; chromatographic eluent, petroleum ether/AcOEt 2:1. Melting point and NMR spectra were identical to those obtained with authentic sample.[12]

1-(2-Amino-5-fluorophenyl)ethanone, 2d: 49 mg, 64%; brown solid; chromatographic eluent, petroleum ether/AcOEt 3:2; R_f = 0.30; mp 64−65 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.52 (s, 3H), 6.00 (br s, 2H), 6.55−6.62 (m, 1H), 6.97−7.07 (m, 1H), 7.32−7.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 116.2, 118.4, 122.2, 122.7, 146.7, 150.9, 199.7; ESI-MS 154 $[M + H]^+$, 176 $[M + Na]^+$. Anal. Calcd for C_8H_8FNO: C, 62.74; H, 5.26; N, 9.15. Found: C, 62.53; H, 5.31; N, 9.08.

Benzyl 3-(2-Aminophenyl)-3-oxopropylcarbamate, 2g: The product has not been isolated but was used as reaction intermediate because of the presence of the *para*-substituted regioisomer that has a very similar retention factor; R_f = 0.45 (petroleum ether/AcOEt 1:1); ESI-MS 299 $[M + H]^+$, 321 $[M + Na]^+$.

Benzyl 3-(2-Amino-5-methylphenyl)-3-oxopropylcarbamate, 2h: 41 mg, 26%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 1:1; R_f = 0.55; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.14−3.20 (t, J = 5.43 Hz, 2H), 3.54−3.62 (t, J = 5.43 Hz, 2H), 5.07 (s, 2H), 5.42 (br s, 1H), 6.54−6.59 (d, J = 8.65 Hz, 1H), 7.07−7.11 (d, J = 8.65 Hz), 7.32 (s, 5H), 7.46 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 37.6, 39.8, 67.2, 116.2, 117.9, 126.8, 127.4, 127.7, 128.3, 129.5, 135.1, 137.1, 145.9, 156.1, 200.6; ESI-MS 335 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.47; H, 6.39; N, 9.16.

Benzyl 3-(2-Amino-5-methoxyphenyl)-3-oxopropylcarbamate, 2i: 67 mg, 41%; brown oil; chromatographic eluent, petroleum ether/AcOEt 1:1; R_f = 0.50; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.13−3.18 (t, J = 5.52 Hz, 2H), 3.54−3.63 (q, J = 5.52 Hz, 2H), 3.75 (s, 3H), 5.07 (s, 2H), 5.42 (bt, J = 5.52 Hz, 1H), 5.94 (br s, 2H), 6.58−6.63 (d, J = 8.88 Hz, 1H), 6.93−6.97 (m, 1H), 7.11−7.13 (m, 1H), 7.32−7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.1, 39.0, 55.9, 66.6, 113.0, 117.3, 118.8, 123.8, 128.0, 128.5, 128.6, 136.5, 145.1, 150.0, 156.4, 200.5; ESI-MS 327 $[M - H]^-$, 329 $[M + H]^+$, 351 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.02; H, 6.31; N, 8.62.

Benzyl 3-(2-Amino-5-fluorophenyl)-3-oxopropylcarbamate, 2j: 54 mg, 34%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 1:1; R_f = 0.45; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.07−3.13 (t, J = 5.64 Hz, 2H), 3.51−3.60 (q, J = 5.64 Hz, 2H), 5.05 (s, 2H), 5.40 (bt, J = 5.64 Hz, 1H), 6.13 (br s, 2H), 6.55−6.61 (m, 1H), 6.96−7.05 (m, 2H), 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.0, 38.9, 66.6, 115.2, 115.6, 118.4, 118.6, 122.5, 123.0, 128.0, 128.4, 136.4, 146.9, 155.6, 201.0; ESI-MS 339 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{17}FN_2O_3$: C, 64.55; H, 5.42; N, 8.86. Found: C, 64.69; H, 5.48; N, 8.77

Benzyl 4-(2-Amino-5-methylphenyl)-4-oxobutylcarbamate, 2k: 56 mg, 34%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84−1.98 (q, J = 6.62 Hz, 2H), 2.24 (s, 3H), 2.92−2.99 (t, J = 6.62 Hz, 2H), 3.22−3.31 (q, J = 6.62 Hz, 2H), 5.08 (s, 2H), 5.08 (br s, 1H), 6.54−6.62 (m, 1H), 6.93−7.10 (m,1H), 7.33 (m, 6H), 7.48 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 24.5, 36.0, 40.6, 66.4, 115.1, 117.4, 124.6, 127.9, 128.3, 128.4, 129.6, 130.5, 136.4, 148.1, 156.4, 201.6; ESI-MS 327 $[M + H]^+$, 349 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.03; H, 6.88; N, 8.41.

Dimethyl 4-Methylquinoline-2,3-dicarboxylate, 3a: 73 mg, 28%; light brown solid; chromatographic eluent, petroleum ether/AcOEt 1:1; mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 7.56−7.60 (t, J = 8.0 Hz, 1H), 7.69−7.73 (t, J = 8.0 Hz, 1H), 7.96−7.98 (d, J = 8.4 Hz, 1H), 8.15−8.17 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 52.4, 52.9, 123.7, 126.8, 127.6, 128.7, 130.4, 130.6, 143.5, 144.6, 145.9, 165.2, 169.9; ESI-MS 260 $[M + H]^+$, 282 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: 64.92; H, 5.13; N, 5.33.

Dimethyl 4,6-Dimethylquinoline-2,3-dicarboxylate, 3b: 183 mg, 67%; brown solid; chromatographic eluent, petroleum ether/AcOEt 1:1; mp 135−138 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.67 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 7.60−7.64 (m, 1H), 7.80 (s, 1H), 8.10−8.15 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.6, 22.1, 52.9, 53.4, 123.0, 127.4, 128.1, 130.7, 133.1, 139.6, 142.8, 143.1, 144.9, 165.4, 168.7; ESI-MS 274 $[M + H]^+$, 296 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: 65.99; H, 5.41; N, 5.30.

Dimethyl 6-Methoxy-4-methylquinoline-2,3-dicarboxylate, 3c: 124 mg, 40%; light brown solid; chromatographic eluent, petroleum ether/AcOEt 1:1; mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 7.21 (s, 1H), 7.42−7.45 (m, 1H), 8.14−8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 52.8, 53.3, 55.7, 101.9, 123.5, 128.0, 129.6, 132.7, 141.5, 142.1, 142.4, 160.0, 165.7, 168.8; ESI-MS 290 $[M + H]^+$, 312 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.09; H, 5.19; N, 4.97.

Dimethyl 6-Fluoro-4-methylquinoline-2,3-dicarboxylate, 3d: 169 mg, 61%; light brown solid; chromatographic eluent, petroleum ether/AcOEt 1:1; mp 93−95 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 7.53−7.69 (m, 2H), 8.22−8.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 53.0, 53.5, 108.2, 121.0, 121.5, 127.9, 129.4, 133.7, 133.9, 143.4, 159.6, 165.4, 168.2; ESI-MS 278 $[M + H]^+$, 300 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{12}FNO_4$: C, 60.65; H, 4.36; N, 5.05. Found: C, 60.78; H, 4.19; N, 5.09.

Dimethyl 4-(2-(Benzyloxycarbonylamino)ethyl)quinoline-2,3-dicarboxylate, 3g: 160 mg, 36%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 3:2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.32−3.39 (t, J = 6.61 Hz, 2H), 3.51−3.58 (q, J = 6.61 Hz, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 5.09 (s, 2H), 5.30 (bt, J = 6.61 Hz, 1H), 6.82−6.86 (m, 1H), 7.31 (m, 5H), 7.70−7.81 (m, 2H), 8.24−8.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.2, 41.4, 53.1, 53.4, 66.7, 119.0, 124.3, 128.1, 128.5, 129.5, 129.7, 131.2, 131.2, 136.3, 136.4, 144.5, 146.9, 156.4, 156.5, 165.6, 168.4; ESI-MS 423 $[M + H]^+$, 445 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.46; H, 5.19; N, 6.77.

Dimethyl 4-(2-(Benzyloxycarbonylamino)ethyl)-6-methylquinoline-2,3-dicarboxylate, 3h: 209 mg, 48%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 3:2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.28−3.36 (t, J = 6.94 Hz, 2H), 3.52−3.61 (q, J = 6.94 Hz, 2H), 3.97 (s, 3H), 4.02 (s, 3H), 5.09 (s, 2H), 5.29 (bt, J = 6.94 Hz, 1H), 7.31 (s, 5H), 7.62−7.67 (d, J = 8.54 Hz, 1H), 8.04 (s, 1H), 8.14−8.18 (d, J = 8.54 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 30.1, 41.3, 53.1, 53.4, 66.6, 123.1, 127.5, 128.0, 128.1, 128.5, 130.9, 133.5, 136.3, 140.2, 143.6, 144.0, 145.4, 156.5, 165.6, 168.6; ESI-MS 437 $[M + H]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.90; H, 5.61; N, 6.38.

Dimethyl 4-(2-(Benzyloxycarbonylamino)ethyl)-6-methoxyquinoline-2,3-dicarboxylate, 3i: 172 mg, 38%; brown oil; chromatographic eluent, petroleum ether/AcOEt 1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.23−3.29 (t, J = 6.90 Hz, 2H), 3.48−3.58(q, J = 6.90 Hz, 2H), 3.96 (s, 3H), 4.01 (s, 3H), 4.04 (s, 3H), 5.09 (s, 2H), 5.26 (bt, J = 6.90 Hz, 1H), 7.36 (m, 5H), 7.44 (m, 1H), 7.71 (m, 1H), 8.15 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.7, 40.9, 52.1, 53.0, 53.3, 56.0, 66.6, 102.1, 124.2, 127.9, 128.0, 128.1, 128.5, 129.2, 132.6, 136.3, 142.0, 142.9, 156.6, 160.4, 165.6, 168.8; ESI-MS 453 $[M + H]^+$, 475 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.64; H, 5.48; N, 6.26.

Dimethyl 4-(2-(Benzyloxycarbonylamino)ethyl)-6-fluoroquinoline-2,3-dicarboxylate, 3j: 185 mg, 42%; orange oil; chromatographic eluent, petroleum ether/AcOEt 1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.26−3.33 (t, J = 6.69 Hz, 2H), 3.49−3.59 (q, J = 6.69 Hz, 2H), 3.97 (s, 3H), 4.03 (s, 3H), 5.10 (s, 2H), 5.24 (bt, J = 6.69 Hz, 1H), 7.31−7.33 (m, 5H), 7.59 (m, 1H), 7.97 (m, 1H), 8.28 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.7, 41.0, 53.2, 53.5, 66.8, 66.9, 108.0, 108.5, 121.4, 122.0, 128.0, 128.1, 128.5, 133.8, 134.0, 136.3, 144.0, 156.5, 159.9, 165.4, 168.2; ESI-MS 441 $[M + H]^+$, 463 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{21}FN_2O_6$: C, 62.72; H, 4.81; N, 6.36. Found: C, 62.58; H, 4.87; N, 6.22.

Dimethyl 4-(3-(Benzyloxycarbonylamino)propyl)-6-methylquinoline-2,3-dicarboxylate, 3k: 158 mg, 35%; yellow oil; chromatographic eluent, petroleum ether/AcOEt 1:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90−1.98 (quintet, J = 7.60 Hz, 2H), 2.56 (s, 3H), 3.05−3.09 (t, J = 7.60 Hz, 2H), 3.26−3.32 (q, J = 7.60 Hz), 3.93 (s, 3H), 4.00 (s, 3H), 5.08 (s, 2H + bt, 1H), 7.27−7.33 (m, 5H), 7.60−7.62 (d, J = 8.40 Hz, 1H) 7.78 (s, 1H), 8.13−8.15 (d, J = 8.40 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 27.0, 30.7, 40.6, 52.9, 53.3, 66.6, 122.8, 126.9, 127.1, 128.0, 128.1, 128.5, 131.0, 133.2, 136.5, 139.8, 144.1, 145.5, 146.3, 156.5, 165.7, 168.7; ESI-MS 451 $[M + H]^+$. Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22. Found: C, 66.74; H, 5.77; N, 6.09.

General Procedure for the Preparation of Lactames 4h−k. Quinolines **3h−k** were treated with 2.5 equiv of potassium carbonate in MeOH at 60 °C under magnetic stirring overnight. Afterward, the solvent was removed under reduced pressure and the residue was washed with chloroform to remove the organic impurities.

Potassium 4-Oxo-1,2,3,4-tetrahydrobenzo[*c*][2,7]naphthyridine-5-carboxylate, 4g: 80 mg, 70%; pale brown solid; mp >300 °C; ^{1}H NMR (200 MHz, D_2O) δ 3.40−3.47 (t, J = 7.00 Hz, 2H), 3.61−3.68 (t, J = 7.00 Hz, 2H), 7.31 (br s, 1H), 7.61−8.19 (m, 4H); ^{13}C NMR (50 MHz, D_2O) δ 24.7, 39.1, 125.4, 126.5, 128.4, 128.8, 129.2, 129.6, 130.3, 137.2, 149.8, 158.8, 171.6; ESI-MS 241 $[M-K]^-$. HRMS (ESI) calcd for $C_{13}H_9N_2O_3K_2^+$ 318.9887, found 318.9883.

Potassium 9-Methyl-4-oxo-1,2,3,4-tetrahydrobenzo[*c*][2,7]naphthyridine-5-carboxylate, 4h: 129 mg, 81%; orange solid; mp >300 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 2.58 (s, 3H), 3.37−3.43 (t, J = 6.80 Hz, 2H), 3.59−3.66 (t, J = 6.80 Hz, 2H), 7.32 (br s, 1H), 7.65−7.96 (m, 3H); ^{13}C NMR (50 MHz, D_2O) δ 24.3, 24.8, 39.0, 119.1, 123.6, 126.3, 126.5, 129.2, 129.7, 131.3, 132.2, 144.5, 166.2, 172.0; ESI-MS 333 $[M + K]^+$, 255 $[M - K]^-$; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_3K_2^+$ 333.0044, found 333.0038.

Potassium 9-Methoxy-4-oxo-1,2,3,4-tetrahydrobenzo[*c*][2,7]naphthyridine-5-carboxylate, 4i: 110 mg, 83%; yellow solid; mp >300 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 3.33−3.39 (t, J = 6.10 Hz, 2H), 3.60−3.66 (t, J = 6.10 Hz, 2H), 3.96 (s, 3H), 7.38−7.95 (m, 3H); ^{13}C NMR (50 MHz, D_2O) δ 24.7, 39.0, 56.5, 103.8, 115.9, 118.7, 124.9, 126.4, 130.2, 143.2, 149.9, 158.5, 166.5, 176.5; ESI-MS 349 $[M + K]^+$, 271 $[M - K]^-$; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_4K_2^+$ 348.9993, found 348.9989.

Potassium 9-Fluoro-4-oxo-1,2,3,4-tetrahydrobenzo[*c*][2,7]naphthyridine-5-carboxylate, 4j: 105 mg, 74%; pale brown solid; mp >300 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 3.28−3.35 (t, J = 6.90 Hz, 2H), 3.60−3.67 (t, J = 6.90 Hz, 2H), 7.28 (br s, 1H), 7.68−8.12 (m, 3H); ^{13}C NMR (50 MHz, D_2O) δ 21.7, 39.1, 118.4, 124.5, 125.3, 128.4, 135.4, 139.2, 145.9, 150.9, 156.5, 166.6, 176.7; ESI-MS 299 $[M + H]^+$; HRMS (ESI) calcd for $C_{13}H_8FN_2O_3K_2^+$ 336.9793, found 336.9788.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: ponticelli@unisi.it.

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■ REFERENCES

(1) (a) Bose, D. S.; Idrees, M.; Jakka, N. M.; Rao, J. V. *J. Comb. Chem.* **2010**, *12*, 100–110. (b) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol,

J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398–3405. (c) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374–2378. (d) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1026. (e) Kalluraya, B.; Sreenivasa, S. *Farmaco* **1998**, *53*, 399–404. (f) Dube, D.; Blouin, M.; Brideau, C.; Chan, C.-C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255–1260.

(2) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825–183.

(3) (a) Nittoli, T.; Dushin, R. G.; Ingalls, C.; Cheung, K.; Brawner Floyd, M.; Fraser, H.; Andrea Olland, A.; Hu, Y.; Grosu, G.; Han, X.; Arndt, K.; Guo, B.; Wissner, A. *Eur. J. Med. Chem.* **2010**, *45*, 1379–1386. (b) Agarwal, P. K.; Sharma, S. K.; Sawant, D.; Kundu, B. *Tetrahedron* **2009**, *65*, 1153–1161. (c) Kim, K.; Wissner, A.; Floyd, M. B., Jr.; Fraser, H. L.; Wang, Y. D.; Dushin, R. G.; Hu, Y.; Olland, A.; Guo, B.; Arndt, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5225–5228 and references cited therein.

(4) (a) Commarieu, A.; Hoelderich, W.; Laffitte, J. A.; Dupont, M.-P. *J. Mol. Catal. A* **2002**, *182*−*183*, 137–141. (b) Boyer, J. L.; Krum, J. E.; Myers, M. C.; Fazal, A. N.; Wigal, C. T. *J. Org. Chem.* **2000**, *65*, 4712–4714. (c) Cui, C.; Wang, X.; Weiss, R. G. *J. Org. Chem.* **1996**, *61*, 1962–1974. (d) Martin, R. *Org. Prep. Proced. Int.* **1992**, *24*, 369–435. (e) Hocking, M. B. *J. Chem. Technol. Biotechnol.* **1980**, *30*, 626–646.

(5) Litvinov, V. P. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: London, 2006; Vol. 91, pp 189−300.

(6) Ferrini, S.; Ponticelli, F.; Taddei, M. *Org. Lett.* **2007**, *9*, 69–72.

(7) Ferrini, S.; Ponticelli, F.; Taddei, M. *J. Org. Chem.* **2006**, *71*, 9217–9220.

(8) Zhu, Q.; Jiang, H.; Li, J.; Zhang, M.; Wang, X.; Qi, C. *Tetrahedron* **2009**, *65*, 4604–4613.

(9) Guerrini, G.; Ponticelli, F. *Eur. J. Org. Chem.* **2010**, 3919–3926.

(10) (a) Abdel-Malik, M. M.; De Mayo, P. *Can. J. Chem.* **1984**, *62*, 1275–1278. (b) Fifolt, M. J.; Olczak, R. T.; Mundhenke, R. F.; Bieron, J. F. *J. Org. Chem.* **1985**, *50*, 4576–4582. (c) Eshghi, H.; Hassankhani, A.; Mosaddegh, E. *J. Chem. Res.* **2006**, 218–219. (d) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636–3646. (e) Roice, M. *Chem.—Eur. J.* **2004**, *10*, 4407–4415.

(11) Anwer, B.; Sged, S. A.; Tanveer, A. F. *Tetrahedron Lett.* **1976**, *36*, 3217–3220.

(12) Zhu, L.; Miao, Z.; Sheng, C.; Guo, W.; Yao, J.; Liu, W.; Che, X.; Wang, W.; Cheng, P.; Zhang, W. *Eur. J. Med. Chem.* **2010**, *45*, 2726–2732.