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Studies on pyrrolidinones. synthesis of fused 1,5-naphthyridines

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This article is dedicated to the memory of co-author Dr. Rufine Akué-Gédu, a dear colleague who contributed much to the chemistry of pyroglutamic derivatives, and who sadly passed away in December 2011, at 43 years

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ABSTRACT

The synthesis of new condensed indolizinediones derived from pyroglutamic acid is described. The Semmler–Wolff transposition of the oxime of these ketones leads to fused dihydro-1,5-naphthyridinones. Easy introduction of side amino chains indicates that potential DNA-intercalating heterocyclic systems fused on 1,5-naphthyridine nucleus could be obtained in these series.

1. Introduction

The benzo[f]indolizinedione skeleton[1] of compounds **1** is a very rich scaffold obtained from pyroglutamic acid.[2] We have previously described that treatment of **1** in acidic[3,4] or basic[4,5] media can lead to allylic dehydration, retro-pinacol, pinacol-like rearrangements, and enamide reactions, which provide a variety of new isoquinolines **2**–**7** or succinimides **8** (Fig. 1). In order to obtain compounds with potential biological properties, we studied the synthesis then the reactivity of new oximes in these series, focusing toward products issued from their Semmler–Wolff rearrangement.

2. Results and discussion

2.1. Synthesis of oximes

The starting ketones **9**–**13** have previously been synthesized from Friedel–Crafts cyclization of the corresponding *N*-substituted pyroglutamic acids.[1a,1f,1i,1l,1m,6] Now, *N*-methylindoles derivatives **14** and **15** were obtained by reacting **12** and **13** with dimethylsulfate in the presence of potassium carbonate. Interestingly, ketone **12** needed only 4 h to deliver 90% of product **14** while ketone **13**, substituted by an electro-donating methoxy group required 24 h to yield the same amount of ketone **15**. Oxime **16** was already described by Martin,[1c] and in analogous series, the OH group of the oxime was generally placed in *anti* position from the aromatic group.[1c,7] We have utilized the conditions described[1c] (hydroxylamine hydrochloride in an EtOH/H_2O/AcONa mixture) to prepare products **16**–**22**. It can be observed in Table 1 that even a little steric hindrance, or the introduction of the methoxy group in **13** and **15**, increased the reaction time (compare entries 4 to 6, 5 to 7, 4 to 5 and 6–7).

While checking reactivity of ketone **23** with the withdrawing *N*-tosyl protecting group,[1m] we found that the main product obtained was the known acid **25**[1m] (85%) accompanied by a low amount of a compound assigned as oxime **24** on the basis of his NMR spectrum (Scheme 2). We have previously described that oxidation of amidoketones, with the same scaffold as compounds **9**–**13**

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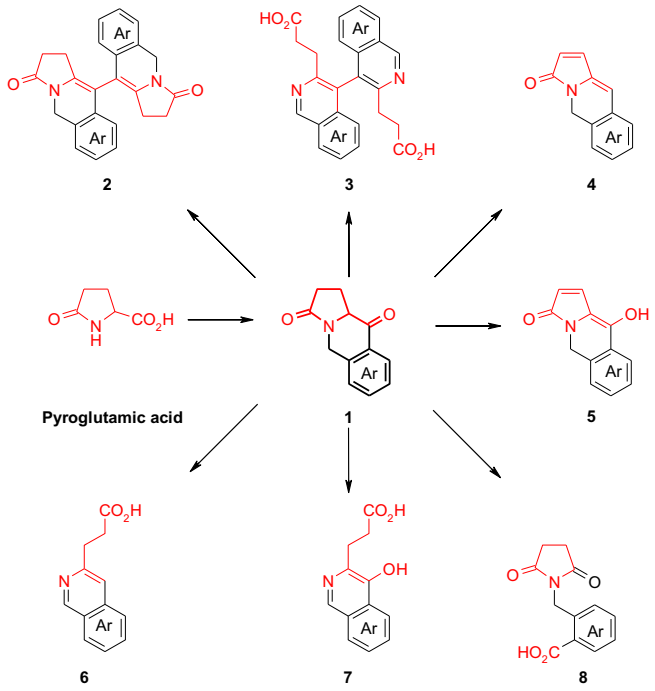
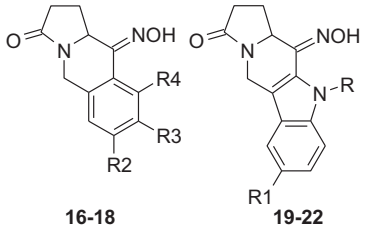


Fig. 1. Some compounds issued from pyroglutamic acid.

Table 1
Synthesis of oximes **16**–**22**



Entry	Oxime	*R*	*R*1	*R*2, *R*3	*R*4	Time (hours)	Yield (%)
1	**16**			H, H	H	5	95
2	**17**			OCH_2O	H	5	92
3	**18**			OCH_3, OCH_3	OH	18	82
4	**19**	H	H			5	75
5	**21**	H	OCH_3			24	78
6	**20**	CH_3	H			24	60
7	**22**	CH_3	OCH_3			48	65

(Scheme 1), in MeOH/MeONa was very fast, ultimately leading to acids **7** (Fig. 1).[1m,5] We thus thought that ketone **23** underwent an oxidation reaction from the oxygen dissolved in EtOH/H_2O. Hydroxyketone **26** thus formed was not isolated. Formation of an *N*-acyliminium salt **27** occurred followed by the opening of the lactam ring to provide iminoketone **28** then hydroxyquinoline **25**. In the same ways as when it was oxidized in MeONa/MeOH solutions,[1m] bubbling nitrogen in the reaction mixture did not avoid oxidation of the starting ketone. It is to be noted that hydrolysis of the tosyl group probably initiated by hydroxylamine, occurred somewhere during this process[8a] (Scheme 2).

In order to increase the chemical diversity for biological testing, oximes ether **29** and **30** were also synthesized. When stirring oxime **16** and benzyl chloride in refluxing acetone, in the presence of potassium carbonate for 30 h, only low yields of desired products were observed along with many by-products. However, by using benzyl bromide in the biphasic water/dichloromethane solvent, tetrabutylammonium hydrogensulfate as a phase transfer agent and sodium hydroxide as the base,[9a] 62% of pure oxime ether **29** was obtained (Scheme 3).

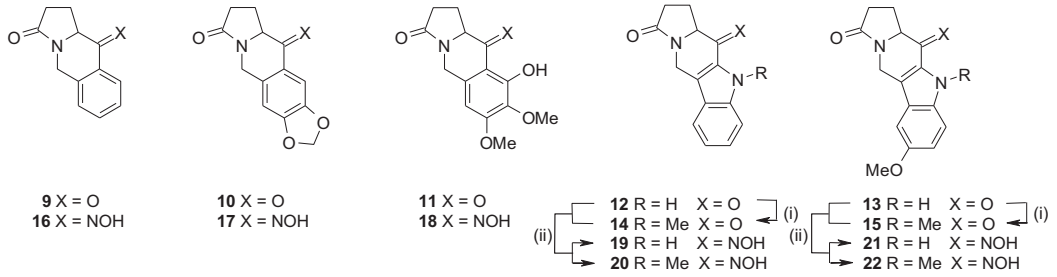
2.2. Semmler–Wolff rearrangement

In the series of fused indolizinediones, treatment of oximes **30** with PPA can led to a Beckman rearrangement (Scheme 4, e.g., lactam **31**),[1e,7,8b] to the formation of a nitrile (e.g., pyrrolinone **32**)[1c,9b] or to a Semmler–Wolff transposition (e.g., tetrahydropyridones **33**).[1c,1e,8b] Noteworthy, the mechanism leading to **32** or **33** involves the formation of a stabilized *N*-acyliminium salt,[10] and in the case of products **33**, is quiet similar to the one leading to compound **28** (Scheme 2).

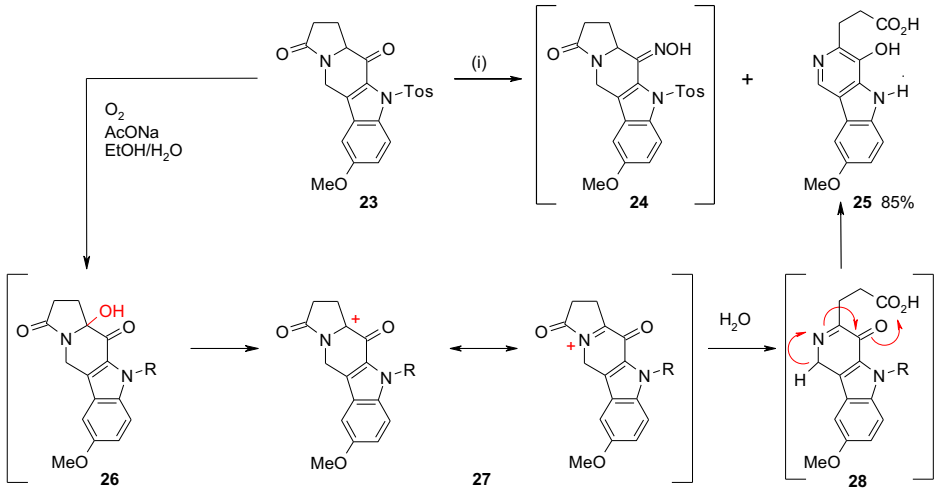
The synthesis of compound **34** described by Martin with 52–63% yields[1c] was repeated in their conditions (PPA, 100 °C).[1c] In our hands, this reaction was irreproducible, with yields ranging from 50% to 75%, and thus we investigate other acidic media. A catalytic amount of triflic acid in trifluoroacetic acid, or Eaton reagent[11,12] led to a reproducible 71–75% yield but the best result was obtained using methanesulfonic acid, neat at 100 °C for 1 h (Table 2, entries 1–4). However, no general conditions were found for the other oximes of the set (Scheme 5), and it proved necessary to adjust the media depending on the substituents present on the aromatic group. For instance, Eaton reagent and oxime **19** gave an irreproducible 85% yield of lactam **37**, while a catalytic amount of triflic acid in methanesulfonic acid led to a reproducible 76% yield of heterocycle **37** (Table 2, entries 7 and 8). Another interest in using mixtures of triflic acid in trifluoroacetic or methanesulfonic acid is the easy quenching of the reaction media when large quantities of oximes were employed. Also, traces of dienes **41**[3,13] (Scheme 5) were sometimes observed in the crude. Finally, thermal transposition of oxime **20** was also checked without interesting results; in one instance only, at a temperature superior to 160 °C, a very few amount of indolodiazepine **42** was observed and characterized by NMR, but we were unable to reproduce this formation.

2.3. Synthesis of fused naphthyridones

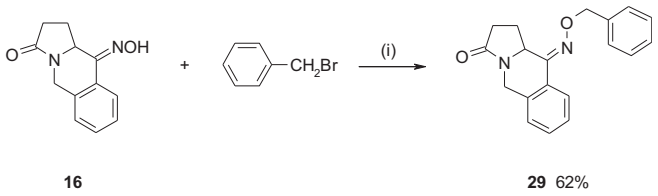
Many fused naphthyridones have already been described,[14] and for some of them with interesting biological properties. We were now interested in aromatizing the previous compounds **34**–**40** in



Scheme 1. Reaction conditions: (i) Me_2SO_4/K_2CO_3/acetone, reflux, 90%; (ii) H_2NOH, HCl/AcONa/EtOH/H_2O, reflux; exact conditions and yields are given in Table 1.



Scheme 2. Reaction conditions: (i) H_2NOH, HCl/AcONa/EtOH/H_2O, reflux 5 h.



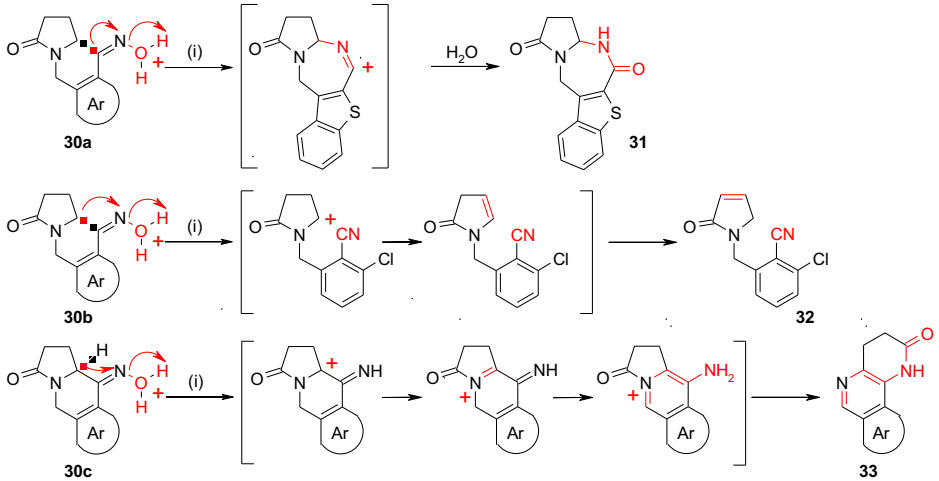
Scheme 3. Reaction conditions: (i) 1 M NaOH, nBu$_4$N$^+$SO$_4$H$^-$, CH_2Cl_2, reflux 12 h.

order to have access to new 2-subtituted compounds with potential DNA-intercallating properties. Many methods are described for the aromatization of dihydropyridones.[15] Bromine in AcONa/AcOH[16a] led only, in an irreproducible manner, to very few amounts of pyridones **43**–**45** from lactams **34**–**36** (Scheme 6), and in the case of indole derivative **37**, its aromatization yielded mixtures of many brominated products. However, when lactam **34** was refluxed with 1.2 equiv of bromine in bromobenzene for 12 h,[16b] 56% of pyridone **43**, accompanied by 31% of a monobrominated compounds **46** (position of the bromine atom was not determined) were obtained; alternatively,[17] by heating **34** with thionyl chloride for 9 h, it furnished a mixture of 21% of pyridone **47** containing a chlorine and a sulfur atom (position of substituents was not determined), and of 34% of chloronaphthyridine **48**. In the same conditions, lactam **37** yielded a small quantity of heterocycle **49** (Scheme 6). This naphthyridone **49** was not obtained by refluxing compound **37** with DDQ[18] in acetic acid or with Pd/C[19] in naphthalene at 175 °C. However, dehydrogenation of dihydropyridones **37**–**40** to fused naphthyridones **49**–**52** proceeded with good yields by refluxing them with selenium oxide[20] in acetic acid for 15–36 h (Scheme 6).

2.4. Synthesis of fused naphthyridines

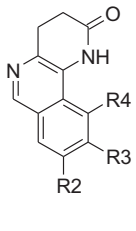
The next step was the synthesis of products substituted by a 2-amino or a 2-methoxy group. They were obtained from precursors prepared by chlorination of the previous naphthyridones **49**–**52**. Refluxing compound **49** in $POCl_3$ for 10 h led to 56% of fused chloropyridine **53**. However, in the same conditions *N*-methyl heterocycle **50** yielded only 5% of **54** after 48 h of reflux. Exchanging phenylphosphonic dichloride[21] for phosphorus oxychloride at 150 °C for 36 h raised the yield to 80%, and working at 180 °C for 15 h in a closed Teflon® bottle allowed the obtention of 85% of heterocycle **54**. These optimized conditions were utilized to obtain products **55** and **56** in good yields (Scheme 7). It is to be noted that the use of $PhPOCl_2$ at 180 °C led to cleaner products than using $POCl_3$ at 110 °C.

Now, naphthyridine **53** was reacted with *N*,*N*-diethylethylenediamine. In refluxing methanol or ethanol, the yield of **57**

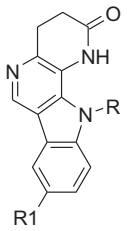


Scheme 4. *Rearrangements of oximes in acidic conditions.* Reaction conditions: (i) PPA, 100–120 °C.

Table 2
Synthesis of fused dihydropyridones

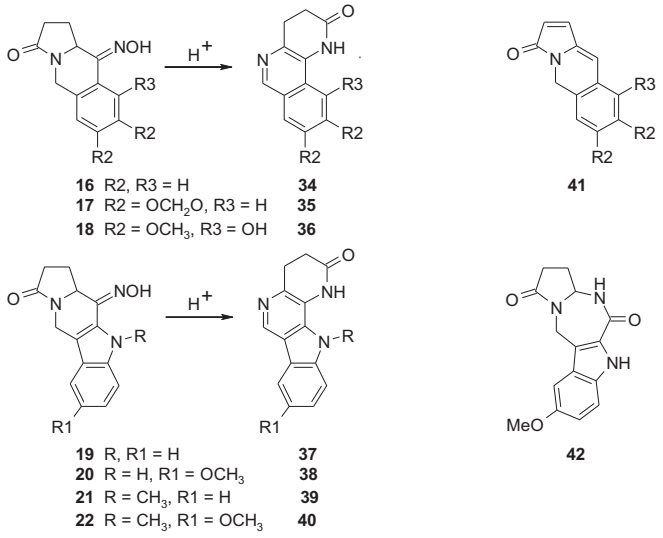


34-36



37-40

Entry	Dihydropyridone	*R*	*R*1	*R*2, *R*3	*R*4	Conditions	Temperature (hours)	Yield (%)
1	**34**			H, H	H	PPA	100 (0.15)	52[1c]
2	**34**			H, H	H	$MeSO_3H/P_2O_5$	100 (0.15)	71
3	**34**			H, H	H	CF_3CO_2H/CF_3SO_3H	72 °C (4)	75
4	**34**			H, H	H	$MeSO_3H$	100 (1)	84
5	**35**			OCH_2O	H	CF_3CO_2H/CF_3SO_3H	72 (4)	81
6	**36**			OCH_3, OCH_3	OH	CF_3CO_2H/CF_3SO_3H	72 (6)	70
7	**37**	H	H			$MeSO_3H/P_2O_5$	100 (1)	85
8	**37**	H	H			$MeSO_3H/CF_3SO_3H$	120 (36)	76
9	**38**	H	OCH_3			CF_3CO_2H/CF_3SO_3H	72 (24)	68
10	**39**	CH_3	H			$MeSO_3H/CF_3SO_3H$	120 (4)	86
11	**40**	CH_3	OCH_3			CF_3CO_2H/CF_3SO_3H	72 (4)	78



Scheme 5. *Synthesis of fused dihydropyridones*. Reaction conditions: See Table 2.

was only 5%, which rose up to 80% when boiling in neat amine (Bp 146 °C) for 24 h. However, in the same conditions compound **54** led only to 45% of product **58** after 72 h. In the same way as for the chlorination, working in a closed Teflon® bottle allow to obtain a better yield (150 °C, 15 h, 85%) of product **58**, and these conditions were utilized to prepare **59** and **60** in good yields (Scheme 7). On the other hand, refluxing chloropyridine **53** in a MeONa/MeOH mixture led quantitatively to fused methoxynaphthyridine **61** (Scheme 7).

3. Conclusion

In this paper, we described the synthesis of new condensed indolizinediones derived from pyroglutamic acid, and the Semmler–Wolff transposition of the oxime of these ketones, which furnished novel heterocyclic scaffolds in the fused naphthyridine series. Noteworthy, the easy introduction of side amino chains indicates that potential DNA-intercalating heterocyclic systems fused on 1,5-naphthyridine nucleus could be obtained in these series.

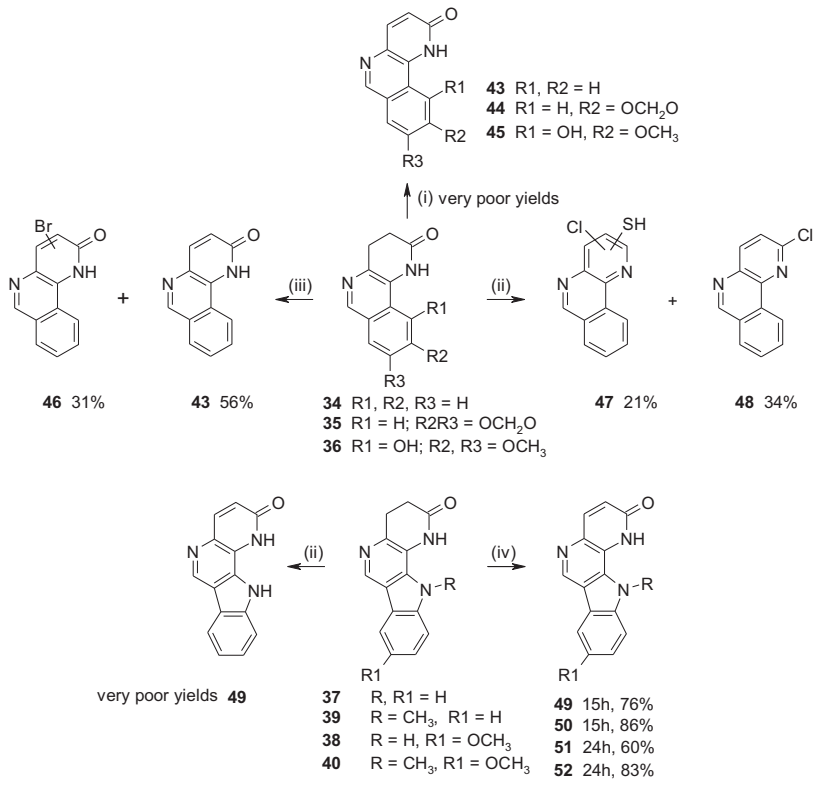
4. Experimental section

4.1. General

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively; noteworthy, NMR spectra of most of the compounds described are strongly dependent on concentration and solvent utilized. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel $60F_{254}$ plates. MS were obtained by LC-MS on a HPLC combined with a Surveyor MSQ (Thermo Electron) equipped with an APCI-source. Microanalyses were performed by the "Service de Microanalyses" of LSEO, Université de Bourgogne, Dijon, France.

4.2. 10-Methyl-5,10-dihydro-1*H*-indolizino[7,6-*b*]indole-3,11(2*H*,11a*H*)-dione (14)

A stirred mixture of ketone **12** (55.6 g, 0.22 mol), potassium carbonate (30.8 g, 0.22 mol) and dimethylsulfate (56.2 g, 0.45 mol) in acetone (300 mL) was refluxed for 4 h. The solid obtained upon evaporation was stirred in dichloromethane. After washing three times with water, the organic phase was dried (Na_2SO_4). The solid obtained was recrystallized from acetone to give 90% of ketone **14** as light brown powder; mp (acetone) 186–188 °C; R_f (EtOAc) 0.6; IR ν (cm^{-1}): 1647, 1610, 1505, 1475; ^1H NMR ($CDCl_3$) δ (ppm): 2.37–2.66 (m, 4H), 4.10 (s, 3H), 4.35–4.45 (m, 1H), 4.41 (d, J=17.7 Hz, 1H), 5.53 (d, J=17.7 Hz, 1H), 7.20 (td, J=7.0, 1.3 Hz, 1H), 7.40 (dt, J=7.0, 1.0 Hz, 1H), 7.47 (td, J=8.2, 1.3 Hz, 1H), 7.64 (dt, J=8.2, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8 (CH_2), 30.2 (CH_2), 31.6 (CH_3), 37.2 (CH_2), 62.7 (CH), 110.5 (CH), 121.0 (CH), 121.2 (CH), 122.7 (CH, C), 125.1 (C), 127.6 (C), 140.3 (C), 174.0 (C), 188.1 (C). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.58; H, 5.87; N, 10.77.



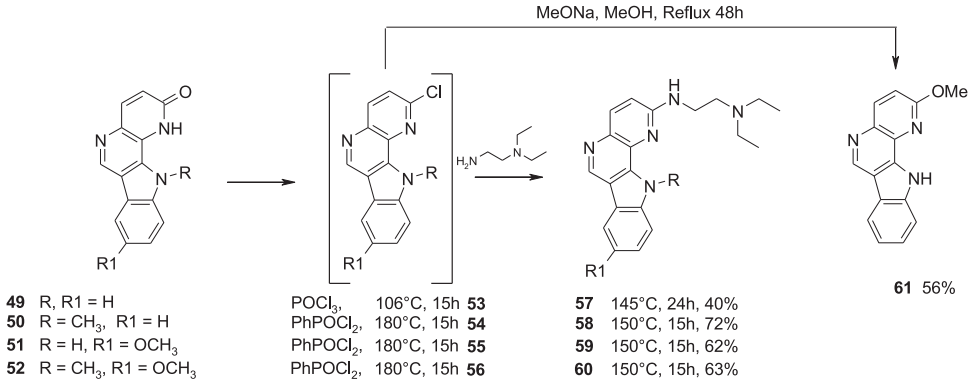
Scheme 6. Reaction conditions: (i) Br_2, AcONa, AcOH, 20 °C, 12 h; (ii) $SOCl_2$, reflux, 12 h; (iii) Br_2, PhBr, reflux, 12 h; (iv) SeO_2, AcOH, reflux.

4.3. 7-Methoxy-10-methyl-5,10-dihydro-1*H*-indolizino[7,6-*b*]indole-3,11(2*H*,11a*H*)-dione (15)

A stirred mixture of ketone **13** (11.6 g, 43 mmol), potassium carbonate (5.9 g, 43 mmol), and dimethylsulfate (10.8 g, 90 mmol) in acetone (200 mL) was refluxed for 4 h. The solid obtained upon evaporation was stirred in dichloromethane. After washing three times with water, the organic phase was dried (Na_2SO_4). The solid obtained was recrystallized from acetone to give 90% of ketone **15** as a white powder; mp (acetone) 188–190 °C; R_f (EtOAc/MeOH 95/5) 0.66; IR ν (cm^{-1}): 1677, 1658, 1505, 1446; ^1H NMR ($CDCl_3$) δ (ppm): 2.34–2.65 (m, 4H), 3.87 (s, 3H), 4.07 (s, 3H), 4.37 (d, J=17.0 Hz, 1H), 4.37–4.48 (m, 1H), 5.48 (d, J=17.0 Hz, 1H), 6.97 (d, J=2.4 Hz, 1H), 7.13 (dd, J=9.1, 2.4 Hz, 1H), 7.29 (d, J=9.1, Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.9 (CH_2), 30.3 (CH_2), 31.8 (CH_3), 37.3 (CH_2), 55.7 (CH_3), 62.8 (CH), 100.4 (CH), 111.7 (CH), 120.0 (CH), 122.8 (C), 124.2 (C), 128.4 (C), 136.1 (C), 154.9 (C), 174.1 (C), 188.0 (C). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.62; H, 5.90; N, 9.69.

4.4. 1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione 10-oxime (16)

A stirred mixture of ketone **9** (20.4 g, 101 mmol), sodium acetate trihydrate (28.9 g, 213 mmol), and hydroxylamine hydrochloride (14.1 g, 203 mmol) in ethanol (160 mL) and water (160 mL) was refluxed for 5 h. The solid obtained upon cooling at room temperature was filtered and the filtrate was partly evaporated to give a solid. The combined solids were washed with cold (4 °C) water, then recrystallized from ethanol to give 95% of oxime **16** as a white powder; mp (ethanol) 215–217 °C (lit.213.5–216[1c]); IR ν (cm^{-1}): 3139, 1648, 1505, 1466; ^1H NMR ($CDCl_3$) δ (ppm): 1.84–2.22 (m, 1H), 2.29–2.72 (m, 2H), 2.86–3.11 (m, 1H), 4.00 (d, J=15.0 Hz, 1H), 4.98 (t, J=8.4 Hz, 1H), 5.13 (d, J=15.0 Hz, 1H), 7.28 (m, 3H), 7.86 (d, J=6.8 Hz, 1H);^{13}C NMR (DMSO-d_6) δ (ppm): 24.5 (CH_2), 30.0 (CH_2), 40.3 (CH_2), 55.0 (CH), 126.4 (CH), 126.9 (CH), 129.7 (C, CH), 134.2 (CH), 135.2 (C), 152.9 (C), 172.4 (C).



Scheme 7. Synthesis and reaction of chloronaphthyridines.

4.5. 9,9a-Dihydro[1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*] isoquinoline-7,10(5*H*,8*H*)-dione 10-oxime (17)

A stirred mixture of ketone **10** (10.0 g, 41 mmol), sodium acetate trihydrate (11.7 g, 86 mmol), and hydroxylamine hydrochloride (5.7 g, 82 mmol) in ethanol (90 mL) and water (90 mL) was refluxed for 5 h. The solid obtained upon cooling at room temperature was filtered, washed with cold (4 °C) water and then recrystallized from ethanol to give 92% of a 80/20 mixture of the two isomers of oxime **17** as a white powder; mp (ethanol) 205–229 °C; IR ν (cm^{-1}): 3260, 1710, 1480, 1230; ^1H NMR ($CDCl_3$) δ (ppm): 1.83–2.11 (m, 1H), 2.27–2.65 (m, 2H), 2.86–3.10 (m, 1H), 3.88 (d, *J*=15.8 Hz, 1H), 4.89 (t, *J*=8.2 Hz, 1H), 5.01 (d, *J*=15.8 Hz, 1H), 5.99 and 6.04 (2s, 80/20, 2H), 6.66 and 6.71 (2s, 80/20, 1H), 7.31 and 7.50 (2s, 80/20, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.6 (CH_2), 30.8 (CH_2), 41.1 (CH_2), 55.7 (CH), 102.3 (CH_2), 104.5 (CH), 107.1 (CH), 123.9 (C), 131.1 (C), 147.7 (C), 149.2 (C), 153.6 (C), 173.1 (C). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.77; H, 4.58; N, 10.75.

4.6. 9-Hydroxy-7,8-dimethoxy-1,10a-dihydropyrrolo[1,2-*b*] isoquinoline-3,10(2*H*,5*H*)-dione 10-oxime (18)

A stirred mixture of ketone **11** (10.0 g, 36 mmol), sodium acetate trihydrate (10.3 g, 76 mmol), and hydroxylamine hydrochloride (5.0 g, 72 mmol) in ethanol (80 mL) and water (80 mL) was refluxed for 18 h. The solid obtained upon cooling at room temperature was filtered, washed with cold (4 °C) water then recrystallized from methanol to give 82% of oxime **18** as white powder; mp (methanol) 140–142 °C; IR ν (cm^{-1}): 3220, 1660, 1550, 1440, 1110; ^1H NMR ($CDCl_3$/CF_3CO_2H) δ (ppm): 2.20–2.46 (m, 1H), 2.55–2.90 (m, 2H), 3.20–3.42 (m, 1H), 3.92 (s, 3H), 4.00 (s, 3H), 4.11 (d, *J*=16.4 Hz, 1H), 5.16 (t, *J*=8.3 Hz, 1H), 5.16 (d, *J*=16.4 Hz, 1H), 6.57 (s, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 25.7 (CH_2), 30.6 (CH_2), 41.1 (CH_2), 55.4 (CH), 56.8 (CH_3), 60.7 (CH_3), 102.4 (CH), 108.2 (CH), 132.1 (C), 136.0 (C), 152.6 (C), 154.8 (C), 157.8 (C), 173.1 (C). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.55; H, 5.51; N, 9.56.

4.7. 5,10-Dihydro-1*H*-indolizino[7,6-*b*]indole-3,11(2*H*,11a*H*)-dione 11-oxime (19)

A stirred mixture of ketone **12** (36.3 g, 150 mmol), sodium acetate trihydrate (46.6 g, 320 mmol), and hydroxylamine hydrochloride (21.8 g, 310 mmol) in ethanol (200 mL) and water (200 mL) was refluxed for 5 h. The solid obtained upon evaporation was washed with cold (4 °C) water, then recrystallized from ethanol to give 75% of a 70/30 mixture of two isomers of oxime **19** as a white powder; mp (ethanol) 212–214 °C; R_f (EtOAc/MeOH 90/10) 0.83; IR ν (cm^{-1}): 3280, 1680; ^1H NMR ($CDCl_3$/CF_3CO_2H) δ (ppm): 2.22–2.53 (m, 1H), 2.65–2.86 (m, 2H), 3.11–3.36 (m, 1H), 4.28 and 4.45 (2d, 30/70, *J*=16.9 and 17.5 Hz, 1H), 4.86 and 5.09 (2t, 70/30, *J*=6.8 and 8.6 Hz, 1H), 5.45 and 5.58 (2d, 70/30, *J*=17.5 and 16.9 Hz, 1H), 7.18–7.30 (m, 1H), 7.40–7.55 (m, 2H), 7.57–7.67 (m, 1H). ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ (ppm) (major isomer): 21.8 (CH_2), 30.1 (CH_2), 37.1 (CH_2), 56.6 (CH), 113.0 (CH), 113.5 (C), 119.1 (CH), 119.7 (C), 122.9 (CH), 124.0 (C), 124.1 (CH), 137.2 (C), 144.4 (C), 173.6 (C). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.83; H, 5.17; N, 16.41.

4.8. 10-Methyl-5,10-dihydro-1*H*-indolizino[7,6-*b*]indole-3,11(2*H*,11a*H*)-dione 11-oxime (20)

A stirred mixture of ketone **14** (56.0 g, 220 mmol), sodium acetate trihydrate (60.0 g, 440 mmol), and hydroxylamine hydrochloride (30.6 g, 440 mmol) in ethanol (600 mL) and water (200 mL) was refluxed for 24 h. The solid obtained upon evaporation was washed with cold (4 °C) water then recrystallized from ethanol to give 60% of oxime **20** as a gray–white powder; mp (ethanol) 243–245 °C; R_f (EtOAc) 0.52; IR ν (cm^{-1}): 3166, 1653, 1594, 1461; ^1H NMR ($CDCl_3$) δ (ppm): 1.97–2.20 (m, 1H), 2.28–2.65 (m, 2H), 3.02–3.21 (m, 1H), 4.01(s, 3H), 4.04 (d, *J*=16.1 Hz, 1H), 4.92 (dd, *J*=7.2, 7.0 Hz, 1H), 5.38 (d, *J*=16.1 Hz, 1H), 7.11 (tdd, *J*=8.1, 5.6, 2.5 Hz, 1H), 7.27 (td, *J*=7.4 Hz, 1H), 7.32 (dd, *J*=8.1, 0.9 Hz, 1H), 7.53 (dt, *J*=7.4, 1.0 Hz, 1H), 10.97 (s, 1H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.3 (CH_2), 29.9 (CH_2), 32.5 (CH_3), 35.3 (CH_2), 55.7 (CH), 110.0 (CH), 114.0 (C), 119.0 (CH), 119.6 (CH), 123.3 (CH), 123.7 (C), 127.6 (C), 138.7 (C), 149.5 (C), 172.5 (C). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 67.01; H, 5.77; N, 15.38.

4.9. 7-Methoxy-5,10-dihydro-1*H*-indolizino[7,6-*b*]indole-3,11(2*H*,11a*H*)-dione 11-oxime (21)

A stirred mixture of ketone **13** (12.0 g, 44 mmol), sodium acetate trihydrate (12.1 g, 90 mmol), and hydroxylamine hydrochloride (6.2 g, 90 mmol) in ethanol (100 mL) and water (50 mL) was refluxed for 24 h. The solid obtained upon evaporation was washed with cold (4 °C) water then recrystallized from EtOAc/MeOH to give 78% of oxime **21** as a white powder; mp (EtOAc/MeOH) 232–234 °C; R_f (EtOAc/MeOH 95/5) 0.58; IR ν (cm^{-1}): 3400, 3300, 1677, 1642, 1500, 1482; ^1H NMR ($CDCl_3$) δ (ppm): 2.43–2.62 (m, 4H), 3.85 (s, 3H), 4.26 (d, *J*=16.7 Hz, 1H), 4.54–4.66 (m, 1H), 5.25 (d, *J*=16.7 Hz, 1H), 6.94 (dd, *J*=9.5, 2.5 Hz, 1H), 6.94 (d, *J*=2.5 Hz, 1H), 7.35 (d, *J*=9.5 Hz, 1H), 10.13 (s, 1H, deuterium oxide exchangeable), 11.34 (s, 1H, deuterium oxide exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.0 (CH_2), 30.1 (CH_2), 37.1 (CH_2), 55.8 (CH_3), 57.4 (CH), 100.8 (CH), 111.7 (CH), 112.1 (CH), 114, 5 (C), 119.9 (C), 126.0 (C), 129.9 (C), 135.5 (C), 154.6 (C), 173.6 (C). Anal. Calcd for $C_{15}H_{15}N_3O_3$, MeOH: C, 61.78; H, 5.69; N, 13.95. Found: C, 62.11; H, 5.34; N, 13.59.

4.10. 7-Methoxy-10-methyl-5,10-dihydro-1*H*-indolizino[7,6-*b*] indole-3,11(2*H*,11a*H*)-dione 11-oxime (22)

A stirred mixture of ketone **15** (10.4 g, 36 mmol), sodium acetate trihydrate (19.8 g, 150 mmol), and hydroxylamine hydrochloride (10.1 g, 150 mmol) in ethanol (150 mL) and water (50 mL) was refluxed for 48 h. The solid obtained upon evaporation was washed with cold (4 °C) water then recrystallized from EtOAc to give 65% of oxime **22** as a white powder; mp (EtOAc) >250 °C; R_f (EtOAc/MeOH 95/5 0.7) 0.83; IR ν (cm^{-1}): 3128, 1652, 1628, 1550; 1495; ^1H NMR ($CDCl_3$) δ (ppm): 2.05–2.25 (m, 1H), 2.32–2.70 (m, 2H), 2.97–3.22 (m, 1H), 3.85 (s, 3H), 3.93 (s, 3H), 4.05 (d, *J*=16.0 Hz, 1H), 4.87–4.98 (dd, *J*=7.2, 7.0 Hz, 1H), 5.41 (d, *J*=16.0 Hz, 1H), 6.95 (s, 1H), 6.98 (dd, *J*=8.8, 2.5 Hz, 1H), 7.21 (dd, *J*=8.8, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2 (CH_2), 30.1 (CH_2), 31.2 (CH_3), 37.8 (CH_2), 55.8 (CH_3), 61.8 (CH), 102.6 (CH), 109.8 (C), 110.2 (CH), 113.4 (CH), 123.1 (C), 125.1 (C), 126.8 (C), 130.4 (C), 154.7 (C), 173.6 (C). Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.87; H, 6.05; N, 13.84.

4.11. 3-(4-Hydroxy-8-methoxy-5*H*-pyrido[4,3-*b*]indol-3-yl) propionic acid (25)

Ketone **23** (13 mg) was reacted with hydroxylamine in the same conditions as for ketone 12. Known acid 25[1m] (85%) was identified by NMR spectrum of the crude reaction mixture.

Acid 25: ^1H NMR ($CDCl_3$/DMSO-d_6) δ (ppm): 2.58 (t, *J*=6.8 Hz, 2H), 3.07 (t, *J*=6.8 Hz, 2H), 7.04 (dd, *J*=9.0, 2.3 Hz, 1H), 7.43 (d, *J*=9.0 Hz, 1H), 7.69 (d, *J*=2.3. Hz, 1H), 8.75 (s, 1H), 8.30 (bs, 1H, OH), 11.50 (bs, 1H, deuterium oxide exchangeable). It contains also a compound with the following H NMR spectrum: ^1H NMR ($CDCl_3$/DMSO-d_6) δ (ppm): 1.83–2.10 (m, 1H), 2.33 (s, 3H), 2.36–2.69 (m, 2H), 2.96–3.15 (m, 1H), 3.83 (s, 3H), 3.85 (d, *J*=16.8 Hz, 1H), 5.01 (t,

J=7.0 Hz, 1H), 5.21 (d, *J*=16.8 Hz, 1H), 6.80 (d, *J*=2.5 Hz, 1H), 7.03 (dd, *J*=9.2, 2.5 Hz, 1H), 7.12 (d, *J*=8.2 Hz, 2H), 8.47 (d, *J*=8.2 Hz, 2H), 8.10 (d, *J*=9.2 Hz, 1H).

4.12. 1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione 10-(*O*-benzyloxime) (29)

A stirred mixture of oxime **16** (0.30 g, 1.38 mmol), benzyl bromide (0.24 g, 1.38 mmol), and tetrabutylammonium hydrogensulfate (0.067 g, 0.2 mmol) in 1 M sodium hydroxide aqueous solution (3 mL) and dichloromethane (3 mL) was refluxed for 12 h. The residue obtained upon evaporation was crystallized from EtOAc to give 62% of oxime benzyl ether **29**, which was only characterized by NMR; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.75–2.08 (m, 1H), 2.25–2.60 (m, 2H), 2.80–3.00 (m, 1H), 3.96 (d, *J*=16.2 Hz, 1H), 4.89 (dd, *J*=6.0, 7.5 Hz, 1H), 5.08 (d, *J*=16.2 Hz, 1H), 5.19 (d, *J*=11.7 Hz, 1H), 5.22 (d, *J*=11.7 Hz, 1H), 7.19 (dd, *J*=1.8, 7.3 Hz, 1H), 7.29 (m, 2H), 7.33–7.43 (m, 5H), 7.92 (dd, *J*=7.3, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 25.1 (CH_2), 30.4 (CH_2), 40.8 (CH_2), 55.7 (CH), 77.1 (CH_2), 124.9 (CH), 126.0 (CH), 127.5 (2 CH), 127.9 (CH), 128.2 (2 CH), 129.6 (2 CH), 134.3 (C), 134.8 (CH), 137.0 (C), 153.4 (C), 173.0 (C).

4.13. 9,9a-Dihydro[1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]isoquinoline-7,10(5*H*,8*H*)-dione 10-(*O*-benzyloxime) (30)

A stirred mixture of oxime **17** (0.30 g, 1.15 mmol), benzyl bromide (0.20 g, 1.15 mmol), and tetrabutylammonium hydrogensulfate (0.067 g, 0.2 mmol) in 1 M sodium hydroxide aqueous solution (3 mL) and dichloromethane (3 mL) was refluxed for 12 h. The residue obtained upon evaporation crystallized from EtOAc to give 67% of oxime benzyl ether **30**; mp (EtOAc) 149–150 °C; IR ν (cm^{-1}): 1681, 1495, 1478, 1456; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.76–2.02 (m, 1H), 2.25–2.58 (m, 2H), 2.78–2.96 (m, 1H), 3.85 (d, *J*=16.4 Hz, 1H), 4.80 (dd, *J*=14.0, 7.3 Hz, 1H), 5.08 (d, *J*=16.4 Hz, 1H), 5.16 (d, *J*=11.9 Hz, 1H), 5.23 (d, *J*=11.9 Hz, 1H), 5.96 (d, *J*=15.6 Hz, 1H), 5.97 (d, *J*=15.6 Hz, 1H), 6.63 (s, 1H), 7.30–7.36 (m, 5H), 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.1 (CH_2), 30.4 (CH_2), 40.8 (CH_2), 55.7 (CH), 77.1 (CH_2), 124.8 (CH), 126.0 (CH), 127.4 (2 CH), 127.8 (CH), 127.9 (CH), 128.2 (2 CH), 129.6 (2 CH), 134.7 (2C), 137.0 (C), 153.4 (C), 173.0 (C). This compound was not submitted for elemental analysis.

4.14. 3,4-Dihydrobenzo[*c*]-1,5-naphthyridin-2(1*H*)-one (34)

Oxime **16** (20 g, 93 mmol) was added to hot (100 °C) methanesulfonic acid (200 mL). The mixture was stirred for 1 h under nitrogen. After cooling at room temperature it was poured on ice, and the aqueous phase was washed with dichloromethane and then 10 M sodium hydroxide aqueous solution was added to pH 2–3. The solid obtained was washed with water to give 84% of dihydronaphthyridone **34** with the same properties as described in literature;[1m] mp (95% EtOH) 228–230 °C (lit. 227–228 °C[1m]); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.87 (t, *J*=7.6 Hz, 2H), 3.35 (t, *J*=7.6 Hz, 2H), 7.62 (td, *J*=6.9, 1.2 Hz, 1H), 7.81 (td, *J*=6.9, 1.2 Hz, 1H), 7.96 (d, *J*=6.9 Hz, 1H), 8.15 (d, *J*=6.9 Hz, 1H), 8.92 (s, 1H), 9.88 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 27.9 (CH_2), 30.7 (CH_2), 119.0 (C), 125.0 (CH), 126.8 (2 CH), 127.5 (CH), 127.8 (C), 130.6 (C), 135.9 (C), 146.0 (CH), 171.9 (C).

4.15. 3,4-Dihydro[1,3]benzodioxolo[5,6-*c*]-1,5-naphthyridin-2(1*H*)-one (35)

Oxime **17** (20 g, 77 mmol) was added to trifluoroacetic acid (60 mL). Triflic acid (0.8 mL, 1.36 g, 9 mmol) was added and the mixture was refluxed for 4 h under nitrogen. The residue obtained upon evaporation was poured in water (80 mL) and the aqueous phase was extracted with dichloromethane then dried (Na_2SO_4). The solid obtained upon evaporation was recrystallized from methanol to give 81% of dihydronaphthyridone **35**; IR ν (cm^{-1}): 3535, 1705, 1630, 1500–1470, 1195; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.78 (t, *J*=7.7 Hz, 2H), 3.34 (t, *J*=7.7 Hz, 2H), 6.40 (s, 2H), 7.74 (s, 1H), 7.96 (s, 1H), 9.09 (s, 1H), 10.82 (bs, 1H, deuterium oxide exchangeable). ^{13}C NMR (DMSO-d_6) δ (ppm): 22.8 (CH_2), 28.9 (CH_2), 97.6 (CH), 103.8 (CH_2), 104.4 (CH), 124.6 (C), 126.1 (C), 127.8 (C), 131.5 (C), 135.4 (CH), 150.1 (C), 155.2 (C), 169.9 (C). Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.31; H, 4.48; N, 11.10.

4.16. 10-Hydroxy-8,9-dimethoxy-3,4-dihydrobenzo[*c*]-1,5-naphthyridin-2(1*H*)-one (36)

Oxime **18** (20 g, 68.5 mmol) was added to trifluoroacetic acid (60 mL). Triflic acid (0.8 mL, 9 mmol) was added and the mixture was refluxed for 6 h under nitrogen. The residue obtained upon evaporation was poured in water (80 mL) and the aqueous phase was extracted with dichloromethane then dried (Na_2SO_4). The solid obtained upon evaporation was recrystallized from methanol to give 70% of dihydronaphthyridone **36**. Mp (methanol) 240–242 °C; IR ν (cm^{-1}): 3110, 3200, 1700, 1600, 1480, 1430, 1200; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.83 (t, *J*=7.8 Hz, 2H), 3.32 (t, *J*=7.8 Hz, 2H), 4.01 (s, 6H), 6.86 (s, 1H), 8.67 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.5 (CH_2), 28.3 (CH_2), 56.2 (CH_3), 60.9 (CH_3), 100.4 (CH), 113.5 (C), 125.0 (C), 126.4 (C), 131.3 (C), 137.6 (C), 140.6 (CH), 145.0 (C), 154.5 (C), 168.9 (C). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 60.93; H, 5.56; N, 9.96.

4.17. 1,3,4,11-Tetrahydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (37)

Oxime **19** (97.2 g, 380 mmol) was added to methanesulfonic acid (500 mL). Triflic acid (3.35 mL, 40 mmol) was added and the mixture was heated at 120 °C for 36 h under nitrogen. After cooling at room temperature, it was poured on ice and then 10 M sodium hydroxide aqueous solution was added to pH 2–3. The solid obtained was washed with water to give 76% of dihydronaphthyridone **37**; yellow powder; mp (MeOH) >250 °C; R_f (MeOH) 0.73; IR ν (cm^{-1}): 3440, 1675, 1645; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.69 (t, *J*=7.3 Hz, 2H), 3.18 (t, *J*=7.3 Hz, 2H), 7.25 (t, *J*=7.6 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.63 (d, *J*=7.6 Hz, 1H), 8.18 (d, *J*=7.6, 1H), 8.91 (s, 1H), 9.96 (bs, 2H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 27.7 (CH_2), 30.6 (CH_2), 111.4 (CH), 118.4 (CH), 119.6 (C), 120.2 (CH), 121.0 (CH), 126.4 (CH), 132.1 (C), 135.5 (C), 137.6 (C), 139.4 (C), 143.4 (C), 170.0 (C). LC-MS (APCI$^+$) *m*/*z* 238.3 (MH^+). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.59; H, 4.81; N, 17.98.

4.18. 8-Methoxy-1,3,4,11-tetrahydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (38)

Oxime **21** (1.5 g, 5.5 mmol) was added to trifluoroacetic acid (8.1 mL). Triflic acid (0.05 mL, 0.5 mmol) was added and the mixture was refluxed for 24 h under nitrogen. After cooling at room temperature, the solution was poured on ice and neutralized with satd. K_2CO_3 solution. The solid obtained was washed with water and then recrystallized from methanol to give 68% of dihydronaphthyridone **36**; yellow powder; mp (methanol) >250 °C; R_f (EtOAc/MeOH 95/5) 0.7; IR ν (cm^{-1}): 3142, 1652, 1633, 1500; 1470; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.68 (t, *J*=8.2 Hz, 2H), 3.17 (t, *J*=8.2 Hz, 2H), 3.86 (s, 3H), 7.05 (dd, *J*=8.8, 2.5 Hz, 1H), 7.50 (d, *J*=8.8 Hz, 1H), 7.72 (d, *J*=2.5 Hz, 1H), 8.88 (s, 1H), 9.98 (bs, 1H, deuterium oxide exchangeable), 11.01 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ (ppm): 25.8 (CH_2), 33.9 (CH_2), 55.6 (CH_3), 103.4 (CH), 112.7 (CH), 115.9 (CH), 119.0 (CH), 121.8 (C), 130.6 (2C), 134.8 (C), 137.0 (C), 138.6 (C), 154.0 (C), 174.9 (C). LC-MS (APCI$^+$) *m*/*z*

266.1 (MH^+). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.70; H, 4.98; N, 15.55.

4.19. 11-Methyl-1,3,4,11-tetrahydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (39)

Oxime **20** (28.2 g, 100 mmol) was added to methanesulfonic acid (135 mL). Triflic acid (0.9 mL, 10 mmol) was added and the mixture was heated at 120 °C for 4 h under nitrogen. After cooling at room temperature, it was poured on ice and then 10 M sodium hydroxide aqueous solution was added to pH 2–3. The solid obtained was washed with water to give 86% of dihydronaphthyridone **39**; yellow powder; mp (EtOH) >250 °C; R_f (MeOH/Et_3N 95/5) 0.7; IR ν (cm^{-1}): 3137, 1647, 1579, 1495; ^1H NMR (DMSO-d_6) δ (ppm): 2.50 (t, J=7.8 Hz, 2H), 2.65 (t, J=7.8 Hz, 2H), 4.10 (s, 3H), 7.28 (t, J=7.6 Hz, 1H), 7.52 (t, J=8.3 Hz, 1H), 7.64 (d J=8.3 Hz, 1H), 8.20 (d, J=7.6, 1H), 8.95 (s, 1H), 9.90 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 28.4 (CH_2), 30.7 (CH_2), 31.6 (CH_3), 109.8 (CH), 119.1 (C), 119.8 (C), 120.2 (CH), 120.4 (CH), 126.7 (CH), 136.1 (C, CH), 140.7 (C), 141.5 (C), 142.3 (C), 170.6 (C). LC-MS (APCI$^+$) m/z 250.2 (MH^+). Anal. Calcd for $C_{15}H_{13}N_3O$, 1/4H_2O: C, 70.43; H, 5.32; N, 16.43. Found: C, 70.18; H, 5.44; N, 16.27.

4.20. 8-Methoxy-11-methyl-1,3,4,11-tetrahydro-2*H*-indolo [3,2-*c*]-1,5-naphthyridin-2-one (40)

Oxime **22** (0.50 g, 2 mmol) was added to trifluoroacetic acid (1.3 mL). Triflic acid (0.01 mL, 0.1 mmol) was added and the mixture was refluxed for 4 h under nitrogen. After cooling at room temperature, the solution was poured on ice and neutralized with a saturated K_2CO_3 aqueous solution. The solid obtained was washed with water then recrystallized from methanol to give 78% of dihydronaphthyridone **40**; yellow powder; mp (MeOH) >250 °C; R_f (EtOAc/MeOH 95/5) 0.65; IR ν (cm^{-1}): 3150, 1655, 1620, 1500, 1475; ^1H NMR (DMSO-d_6) δ (ppm): 2.82 (t, J=7.5 Hz, 2H), 3.33 (t, J=7.5 Hz, 2H), 3.93 (s, 3H), 4.10 (s, 3H), 7.16 (dd, J=9.0, 2.5 Hz, 1H), 7.30 (d, J=9.0 Hz, 1H), 7.55 (d J=2.5 Hz, 1H), 7.86 (bs, 1H, deuterium oxide exchangeable), 8.88 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 28.4 (CH_2), 30.7 (CH_2), 31.6 (CH_3), 55.8 (CH_3), 95.4 (CH), 104.6 (CH), 112.7 (C), 115.4 (CH), 120.0 (CH), 130.6 (C), 138.2 (C), 141.5 (C), 141.8 (C), 144.3 (C), 154.1 (C), 170.6 (C). Anal. Calcd for $C_{16}H_{15}N_3O_2$, 1/3H_2O: C, 66.89; H, 5.50; N, 14.62. Found: C, 67.97; H, 5.69; N, 14.50.

4.21. 2-Methoxy-5,7,7a,8,9,12-hexahydropyrrolo[1′,2′:1,2][1,3] diazepino[5,6-*b*]indole-6,10-dione (42)

This compound was observed by ^1H NMR in an attempt to transpose thermally oxime **20** at a temperature superior to 160 °C. ^1H NMR ($CDCl_3$) δ (ppm): 2.30–2.80 (m, 4H), 3.86 (s, 3H), 4.62 (d, J=17.9 Hz, 1H), 5.27–5.43 (m, 1H), 5.36 (d, J=17.9 Hz, 1H), 6.35 (bs, 1H), 6.96 (d, J=2.5 Hz, 1H), 7.05 (dd, J=9.2, 2.5 Hz, 1H), 7.33 (d, J=9.2 Hz, 1H), 9.05 (bs, 1H, deuterium oxide exchangeable).

4.22. Benzo[*c*]-1,5-naphthyridin-2(1*H*)-one (43) and monobrominated compound 46

A stirred mixture of dihydropyridone **34** (0.250 g, 1.3 mmol) and bromine (0.08 mL, 1.6 mmol) in bromobenzene (5 mL) was refluxed for 12 h. The solid obtained after cooling at room temperature and partial evaporation was stirred in an aqueous saturated solution of sodium hydrogen sulfite and then separated by chromatography on SiO_2 (CH_2Cl_2/MeOH 98/2) to give 56% of naphthyridone **43** and of bromonaphthyridone **46**.

Pyridone 43: light brown solid, 56%; mp (CH_2Cl_2) 200–202 °C; R_f (CH_2Cl_2) 0.3; IR ν (cm^{-1}): 1650, 1629, 1581; ^1H NMR ($CDCl_3$) δ (ppm): 7.02 (d, J=9.6 Hz, 1H), 7.82 (t. J=7.5 Hz, 1H), 8.01 (t. J=7.9 Hz, 1H), 8.09 (d. J=7.9 Hz, 1H), 8.23 (d, J=9.6 Hz, 1H) 8.93(d. J=8.4 Hz, 1H), 9.11 (s, 1H), 13.78 (bs, 1H, deuterium oxide exchangeable). ^{13}C NMR ($CDCl_3$) δ (ppm): 121.6 (CH), 123.1 (CH), 125.1 (C), 128.6 (CH), 128.7 (C), 129.4 (CH), 131.2 (C), 131.4 (C), 131.7 (CH), 143.7 (CH), 148.9 (CH), 164.5 (C). Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.17; H, 4.51; N, 13.97.

Bromopyridone 46: light brown solid, 31%; R_f 0.5 (CH_2Cl_2); ^1H NMR ($CDCl_3$/CF_3COOH) δ (ppm): 8.22 (t. J=7.9 Hz, 1H), 8.46 (t. J=7.9 Hz, 1H), 8.60 (d. J=7.9 Hz, 1H), 8.86 (d. J=7.9 Hz, 1H), 8.97 (s, 1H), 9.81 (s, 1H). LC-MS (APCI$^+$) m/z 275.2 and 277.2 (MH^+). This compound was not subjected to elemental analysis.

4.23. Heterocycle 47 and 2-chlorobenzo[*c*]-1,5-naphthyridine (48)

A stirred mixture of dihydropyridone **34** (0.36 g, 0.13 mmol) in thionyl chloride (11 mL) was refluxed for 9 h. The solid obtained after cooling at room temperature and evaporation was stirred in a satd solution of sodium hydrogen carbonate and dichloromethane. The organic phase was dried (Na_2SO_4), and the residue obtained upon evaporation was stirred in ethyl acetate (15 mL) for 1 h. The solid obtained upon filtration was heterocycle **47**, and the solution contains the naphthyridine **48**.

Heterocycle 47: light brown solid, 21%; mp (EtOAc) 216–218 °C; IR ν (cm^{-1}): 1663, 1573, 1491, 1443; ^1H NMR ($CDCl_3$/CF_3CO_2H) δ (ppm): 8.06 (t, J=8.0 Hz, 1H), 8.42 (t. J=8.0 Hz, 1H), 8.50 (d. J=8.0 Hz, 1H), 8.90 (s, 1H), 9.35 (d, J=8.0 Hz, 1H) 9.74 (s, 1H). Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.42; H, 2.86; N, 11.35. Found: C, 58.41; H, 2.54; N, 11.65.

Chloropyridone 48: light brown solid, 34%; purified by chromatography on SiO_2 (EtOAc/Heptane 50/50); mp (EtOAc) 178–180 °C; IR ν (cm^{-1}): 1609, 1490, 1439; ^1H NMR ($CDCl_3$) δ (ppm): 7.68 (d, J=8.5 Hz, 1H), 7.82 (t, J=7.5 Hz, 1H), 7.99 (t, J=7.5 Hz, 1H), 8.09 (d, J=7.5 Hz, 1H), 8.41 (d, J=8.5 Hz, 1H), 9.11 (d, J=7.5 Hz, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 124.2 (CH), 125.8 (CH), 127.1 (CH), 128.4 (C), 131.8 (CH), 131.9 (CH), 133.2 (C), 134.8 (CH), 137.5 (C), 140.8 (C), 149.5 (CH), 153.8 (C). LC-MS (APCI$^+$) m/z 215.2 and 217.4 (MH^+); 256.2 and 258.0 (M^++MeCN).

4.24. 1,11-Dihydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (49)

A stirred mixture of dihydropyridone **37** (20.0 g, 85 mmol) and selenium dioxide (9.5 g, 85 mmol) in acetic acid (300 mL) was refluxed for 15 h. The solid obtained after cooling at room temperature and evaporation was refluxed in water for 30 min. The solid obtained after cooling at room temperature and filtration was purified by chromatography on SiO_2 (EtOAc/MeOH 70/30) to give 76% of naphthyridone **49**; yellow powder; mp (MeOH) >250 °C; R_f (EtOAc/MeOH 70/30) 0.6; IR ν (cm^{-1}): 3335, 3310, 1665, 1610, 1590, 1537, 1510; ^1H NMR (DMSO-d_6) δ (ppm): 6.72 (d, J=9.8 Hz, 1H), 7.35 (t, J=7.6 Hz, 1H), 7.55 (t, J=7.6 Hz, 1H), 7.78 (d, J=8.3 Hz, 1H), 8.10 (d, J=9.8 Hz, 1H), 8.31 (d, J=8.3 Hz, 1H), 9.28 (s, 1H), 11.66 (bs, 1H, deuterium oxide exchangeable), 11.85 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 112.4 (CH), 119.4 (C), 121.1 (2 CH), 122.8 (C), 123.0 (CH), 127.1 (CH), 130.6 (C), 132.2 (C), 136.9 (C), 138.8 (CH), 139.4 (C), 142.6 (CH), 161.4 (C). Anal. Calcd for $C_{14}H_9N_3O$: C, 66.41; H, 4.38; N, 16.59. Found: C, 66.53; H, 4.03; N, 16.47.

4.25. 11-Methyl-1,11-dihydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (50)

A stirred mixture of dihydropyridone **39** (22.0 g, 90 mmol) and selenium dioxide (9.7 g, 90 mmol) in acetic acid (200 mL) was refluxed for 36 h. The solid obtained after cooling at room

temperature and evaporation was refluxed in water for 30 min. The solid obtained after cooling at room temperature and filtration was purified by chromatography on SiO_2 (EtOAc/MeOH 95/5) to give 86% of naphthyridone **50**; yellow powder; mp (MeOH) >250 °C; R_f (EtOAc/MeOH 95/5) 0.76; IR ν (cm^{-1}): 3132, 1658, 1633, 1550, 1500, 1446; ^1H NMR (DMSO-d_6/$CDCl_3$) δ (ppm): 4.60 (s, 3H), 7.09 (d, J=9.2 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 7.60 (td, J=7.7, 1.2 Hz, 1H), 7.76 (d, J=8.3 Hz, 1H), 8.32 (d, J=9.2 Hz, 1H), 8.35 (d, J=8.1 Hz, 1H), 9.45 (s, 1H), 11.39 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 32.3 (CH_3), 110.3 (CH), 113.8 (C), 117.4 (C), 120.2 (CH), 120.7 (CH), 120.8 (CH), 126.1 (CH), 131.2 (C), 135.9 (C), 137.4 (C), 140.7 (CH), 141.0 (CH), 141.2 (C), 160.5 (C). Anal. Calcd for $C_{15}H_{11}N_3O$, ½H_2O: C, 66.76; H, 4.68; N, 16.27. Found: C, 66.90; H, 4.66; N, 16.24.

4.26. 8-Methoxy-1,11-dihydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (51)

A stirred mixture of dihydropyridone **38** (0.9 g, 3.5 mmol) and selenium dioxide (0.39 g, 3.5 mmol) in acetic acid (30 mL) was refluxed for 24 h. The solid obtained after cooling at room temperature and evaporation was refluxed in water for 30 min. The solid obtained after cooling at room temperature and filtration was purified by chromatography on SiO_2 (EtOAc/MeOH 95/5) to give 60% of naphthyridone **51**; yellow powder; mp (EtOH) >250 °C; R_f (EtOAc/MeOH 95/5) 0.7; IR ν (cm^{-1}): 3344, 1677, 1638, 1588, 1485; ^1H NMR (DMSO-d_6/$CDCl_3$) δ (ppm): 3.88 (s, 3H), 6.67 (d, J=9.3 Hz, 1H), 7.13 (dd, J=8.8, 2.3 Hz, 1H), 7.63 (d, J=8.8 Hz, 1H), 7.80 (d, J=2.3 Hz, 1H), 8.04 (d, J=9.3 Hz, 1H), 9.26 (s, 1H), 11.47 (bs, 1H, deuterium oxide exchangeable), 11.83 (bs, 1H, deuterium oxide exchangeable). ^{13}C NMR (DMSO-d_6) δ (ppm): 65.1 (CH_3), 103.4 (CH), 113.6 (CH), 117.2 (CH), 119.8 (C), 121.9 (C), 123.0 (C), 123.2 (CH), 131.2 (C), 132.2 (C), 134.5 (CH), 139.4 (C), 143.1 (CH), 155.0 (C), 161.7 (C). Anal. Calcd for $C_{15}H_{11}N_3O_2$, H_2O: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.50; H, 5.06; N, 14.45.

4.27. 8-Methoxy-11-methyl-1,11-dihydro-2*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-one (52)

A stirred mixture of dihydropyridone **40** (0.25 g, 0.9 mmol) and selenium dioxide (0.1 g, 0.9 mmol) in acetic acid (30 mL) was refluxed for 24 h. The solid obtained after cooling at room temperature and evaporation was refluxed in water for 30 min. The solid obtained after cooling at room temperature and filtration was purified by chromatography on SiO_2 (EtOAc/MeOH 95/5) to give 83% of naphthyridone **52**; yellow powder; mp (MeOH) >250 °C; R_f (EtOAc/MeOH 95/5) 0.75; ^1H NMR ($CDCl_3$) δ (ppm): 3.76 (s, 3H), 3.95 (s, 3H), 6.99 (d, J=9.1 Hz, 1H), 7.20 (dd, J=8.7, 2.3 Hz, 1H), 7.54 (d, J=8.7 Hz, 1H), 7.73 (d, J=2.3 Hz, 1H), 8.25 (d, J=9.1 Hz, 1H), 9.30 (s, 1H). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 69.07; H, 5.04; N, 14.87.

4.28. *N*,*N*-Diethyl-*N*′-11*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-ylethane-1,2-diamine (57)

A stirred solution of dihydropyridone **49** (7.80 g, 33.4 mmol) in phosphorus oxychloride (30 mL) was refluxed for 10 h. The residue obtained upon evaporation was stirred with a saturated aqueous potassium carbonate solution. The solid obtained was washed with water and then recrystallized from EtOH to give 56% of chloronaphthyridine **53**; light brown powder; mp (EtOH) >250 °C; R_f (EtOAc/heptane/Et_3N (5 drops) 50/50) 0.65; IR ν (cm^{-1}): 3400, 1630; 1600; 1505; ^1H NMR ($CDCl_3$) δ (ppm): 7.45 (td, J=7.5, 1.3 Hz, 1H), 7.59 (td, J=7.6, 1.3 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.70 (ddd, J=8.1, 1.2, 0.8 Hz, 1H), 8.27 (ddt, J=7.9, 1.2, 0.8 Hz, 1H), 8.49 (d, J=8.8 Hz, 1H), 9.60 (s, 1H), 9.84 (bs, 1H, deuterium oxide exchangeable). ^{13}C NMR (DMSO-d_6) δ (ppm): 112.9 (CH), 118.4 (C), 120.5 (2 CH), 120.6 (C), 121.5 (C), 123.9 (CH), 126.2 (CH), 134.0 (C), 139.3 (2C), 140.7 (CH), 145.8 (CH), 147.7 (C). A mixture of this intermediate **53** (1.0 g, 4 mmol) in *N*,*N*-diethylethylenediamine (4.6 g, 39 mmol) was refluxed for 24 h. Upon cooling at room temperature, the solution was washed with water, diethyl ether was added and the organic phase was washed with water. The solid obtained upon drying (Na_2SO_4) and evaporation was recrystallized from EtOAc to give 80% of aminonaphthyridine **57**; slightly brown powder; mp (EtOAc) 150–152 °C; R_f (MeOH/Et_3N 95/5) 0.65; IR ν (cm^{-1}): 3680, 3400, 1610, 1530, 1482; ^1H NMR ($CDCl_3$) δ (ppm): 1.09 (t, J=7.1 Hz, 6H), 2.66 (q, J=7.1 Hz, 4H), 2.80 (t, J=5.8 Hz, 2H), 3.68 (q, J=5.8 Hz, 2H), 5.53 (t, J=4.0 Hz, 1H, deuterium oxide exchangeable), 6.88 (d, J=8.9 Hz, 1H), 7.35 (td, 1H, J=7.3, 1.3 Hz, 1H), 7.49 (td, J=7.3, 1.2 Hz, 1H), 7.61 (d, J=8.2 Hz, 1H), 8.17 (d, J=8.9 Hz, 1H), 8.20 (dt, J=7.3, 1.0 Hz, 1H), 9.28 (s, 1H), 9.80 (bs, 1H, deuterium oxide exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 12.6 (2 CH_3), 39.8 (CH_3), 47.4 (2 CH_2), 52.7 (CH_2), 113.1 (CH), 115.0 (CH), 118.4 (CH), 121.0 (CH), 121.2 (C), 126.5 (CH), 133.6 (C), 136.8 (C), 138.4 (CH), 139.1 (CH), 139.8 (C), 140.0 (C), 140.2 (CH), 157.3 (C). Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 71.78; H, 7.30; N, 20.96.

4.29. *N*,*N*-Diethyl-*N*′-(11-methyl-11*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-yl)ethane-1,2-diamine (58)

A Teflon® bottle was charged with a stirring bar, naphthyridone **50** (3.0 g, 12 mmol) and phenylphosphonic dichloride (8.5 mL, 60 mmol). The closed bottle was placed in a heating bath (180 °C), and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water (100 mL) and then refluxed for 1 h. The solution obtained upon filtration was basified then extracted with dichloromethane. The residue obtained upon drying (Na_2SO_4) and evaporation was purified by chromatography on SiO_2 (EtOAc) to give 85% of intermediate **54**; light brown powder; mp (EtOH) 192–194 °C; R_f (EtOAc/heptane/Et_3N (5 drops) 50/50) 0.5; IR ν (cm^{-1}): 1632, 1620, 1500, 1485; ^1H NMR ($CDCl_3$) δ (ppm): 4.65 (s, 3H), 7.45–7.55 (m, 1H), 7.65–7.75 (m, 3H), 8.28 (d, J=7.5 Hz, 1H), 8.47 (d, J=8.3 Hz, 1H), 9.57 (s, 1H). A Teflon® bottle was charged with this intermediate **54** (0.5 g, 1.9 mmol), a stirring bar and *N*,*N*-diethylethylenediamine (0.25 g, 2.2 mmol). The closed bottle was placed in a heating bath (150 °C) and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water (30 mL), the solid obtained was filtered, washed with water then recrystallized from EtOAc to give 80% of aminonaphthyridine **58**; slightly brown powder; mp (EtOAc) >250 °C; R_f (MeOH/Et_3N 95/5) 0.65; IR ν (cm^{-1}): 3680, 3400, 1633, 1603, 1549, 1495; ^1H NMR ($CDCl_3$) δ (ppm): 1.09 (t, J=7.1 Hz, 6H), 2.66 (q, J=7.1 Hz, 4H), 2.80 (t, J=5.8 Hz, 2H), 3.68 (q, J=5.8 Hz, 2H), 4.70 (s, 3H), 5.50 (bq, J=5.5 Hz, 1H, deuterium oxide exchangeable), 6.84 (d, J=8.9 Hz, 1H), 7.40 (td, J=7.4, 1.3 Hz, 1H), 7.63 (bd, J=8.2 Hz, 2H), 8.20 (d, J=8.9 Hz, 1H, ArH), 8.25 (dt, J=7.4, 1.0 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 11.5 (2 CH_3), 32.3 (CH_3), 39.3 (CH_2), 46.6 (2 CH_2), 51.4 (CH_2), 109.3 (CH), 112.7 (CH), 117.7 (C), 119.8 (CH), 120.4 (CH), 121.5 (C), 125.5 (CH), 134.1 (CH), 137.1 (C), 137.4 (C), 138.3 (CH), 139.7 (CH), 140.8 (CH), 155.1 (C). Anal. Calcd for $C_{21}H_{25}N_5$, ¼H_2O: C, 71.66; H, 7.30; N, 19.90. Found: C, 71.91; H, 7.38; N, 19.67.

4.30. *N*,*N*-Diethyl-*N*′-(8-methoxy-11*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-yl)ethane-1,2-diamine (59)

A Teflon® bottle was charged with a stirring bar, naphthyridone **51** (1.0 g, 3.8 mmol) and phenylphosphonic dichloride (2.7 mL, 18.8 mmol). The closed bottle was placed in a heating bath (180 °C) and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water

(30 mL) and then refluxed for 1 h. The solution obtained upon filtration was basified with a saturated aqueous potassium carbonate solution then extracted with dichloromethane. The residue obtained upon drying (Na_2SO_4) and evaporation was purified by chromatography on SiO_2 (EtOAc) to give 80% of intermediate **55**; slightly brown powder; mp (EtOH) >250 °C; R_f (EtOAc) 0.5; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.99 (s, 3H), 7.21 (dd, J=8.6, 2.5 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 7.62 (dd, J=8.6 Hz, 1H), 7.68 (d, J=2.5 Hz, 1H), 8.48 (d, J=8.6 Hz, 1H), 9.54 (s, 1H). A Teflon® bottle was charged with a stirring bar, intermediate **55** (1.0 g, 3.5 mmol) and *N*,*N*-diethylethylenediamine (4.1 g, 35.2 mmol). The closed bottle was placed in a heating bath (150 °C) and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water (40 mL), the solid obtained was filtered, washed with water then recrystallized from EtOAc to give 77% of aminonaphthyridine **59**; slightly brown powder; mp (EtOAc) 145–147 °C; R_f (MeOH/Et_3N 95/5) 0.7; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.09 (t, J=7.1 Hz, 6H), 2.66 (q, J=7.1 Hz, 4H), 2.80 (bt, J=5.8 Hz, 2H), 3.62 (q, J=5.8 Hz, 2H), 3.95 (s, 3H), 5.60 (bq, J=5.5 Hz, 1H, deuterium oxide exchangeable), 6.87 (d, J=9.1 Hz, 1H), 7.09 (dd, J=8.8, 2.2 Hz, 1H), 7.43 (d, J=8.8 Hz, 1H), 7.62 (d, J=2.2 Hz, 1H), 8.16 (d, J=8.9 Hz, 1H), 9.22 (s, 1H), 10.39 (bs, 1H, deuterium oxide exchangeable). Anal. Calcd for $C_{21}H_{25}N_5O$: C, 69.40; H, 6.93; N, 19.27. Found: C, 69.21; H, 7.09; N, 19.55.

4.31. *N*,*N*-Diethyl-*N′*-(8-methoxy-11-methyl-11*H*-indolo[3,2-*c*]-1,5-naphthyridin-2-yl)ethane-1,2-diamine (60)

A Teflon® bottle was charged with a stirring bar, naphthyridone **52** (1.0 g, 3.6 mmol) and phenylphosphonic dichloride (2.6 mL, 18 mmol). The closed bottle was placed in a heating bath (180 °C) and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water (30 mL) and then refluxed for 1 h. The solution obtained upon filtration was basified with a saturated aqueous potassium carbonate solution then extracted with dichloromethane. The residue obtained upon drying (Na_2SO_4) and evaporation was purified by chromatography on SiO_2 (EtOAc) to give 83% of chloronaphthyridine **56**; slightly brown powder; mp (EtOH) >250 °C; R_f (EtOAc) 0.65; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.98 (s, 3H), 4.10 (s, 3H), 7.16 (dd, J=8.6, 2.5 Hz, 1H), 7.52–7.69 (m, 3H), 8.42 (d, J=8.6 Hz, 1H), 9.53 (s, 1H). A Teflon® bottle was charged with a stirring bar, intermediate **56** (1.0 g, 3.4 mmol) and *N*,*N*-diethylethylenediamine (3.9 g, 33.5 mmol). The closed bottle was placed in a heating bath (150 °C) and the mixture was stirred for 15 h. Upon cooling at room temperature, the reaction mixture was added to water (40 mL), the solid obtained was filtered, washed with water then recrystallized from EtOAc to give 76% of aminonaphthyridine **60**; slightly brown powder; mp (EtOAc) 188–190 °C; R_f (MeOH/Et_3N 95/5) 0.75; ^{1}H NMR ^{1}H ($CDCl_3$) δ (ppm): 1.10 (t, J=7.1 Hz, 6H), 2.23 (q, J=7.1 Hz, 4H), 2.80 (bt, J=5.9 Hz, 2H), 3.77 (bq, J=5.9 Hz, 2H), 3.97 (s, 3H), 4.38 (s, 3H), 6.56 (bt, J=5.6 Hz, 1H, deuterium oxide exchangeable), 6.90 (d, J=8.9 Hz, 1H), 7.23 (dd, J=8.8, 2.4 Hz, 1H); 7.53 (d, J=8.8 Hz, 1H); 7.86 (d, J=2.4 Hz, 1H); 8.15 (d, J=8.9 Hz, 1H); 9.43 (s, 1H). Anal. Calcd for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55. Found: C, 70.34; H, 7.29; N, 18.17.

4.32. 2-Methoxy-11*H*-indolo[3,2-*c*]-1,5-naphthyridine (61)

Intermediate **53** was obtained in the same ways as for the synthesis of **57**; a mixture of this intermediate **53** (5.0 g, 19.7 mmol) and 30% MeONa in MeOH (7.9 mL, 79 mmol) in MeOH (100 mL) was refluxed for 48 h. Upon cooling at room temperature, the solution was concentrated, the residue was dissolved in dichloromethane and then washed with water. The solid obtained upon drying (Na_2SO_4) and evaporation was recrystallized from MeOH to give 98% of methoxynaphthyridine **61**; slightly brown powder; mp (MeOH) >250 °C; R_f (MeOH) 0.6; IR ν (cm^{-1}): 3400, 1613, 1515, 1490; ^{1}H NMR ^{1}H ($CDCl_3$) δ (ppm): 4.23 (s, 3H), 7.51 (d, J=9.2 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.70 (t, J=8.1 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 8.48 (d, J=7.5 Hz, 1H), 8.59 (d, J=9.2 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 55.3 (CH_3), 114.3 (CH), 117.7 (CH), 118.7 (C), 122.5 (C), 122.7 (CH), 123.7 (C), 134.1 (CH), 129.3 (C), 129.8 (CH), 130.5 (CH), 133.3 (C), 137.0 (C), 141.4 (CH), 142.7 (CH), 163.4 (C). Anal. Calcd for $C_{15}H_{11}N_3O$, H_2O: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.06; H, 4.96; N, 15.79.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.056. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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