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Synthesis of furo[2,3-*c*]-2,7-naphthyridine derivatives via domino heterocyclization reaction

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Abstract—2-Amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles were found to react with substituted oxiranes yielding 5,6-diamino-8-dialkylamino-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitriles. The oxirane ring was shown to be opened selectively from the unsubstituted side and further cyclization occurred with participation of 3-CN, but not 5-CN of the starting pyridines. The furonaphthyridines obtained were converted into 2-dialkylamino-5-methyl-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitriles and 2-dialkylamino-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitriles by treatment with acetic anhydride and cyclohexanone, respectively. The structure of prepared compounds was confirmed unambiguously by X-ray crystallographic study.

1. Introduction

Furo[2,3-*c*]-2,7-naphthyridine is a rare and uninvestigated heterocyclic system. To date only four derivatives of this framework have been reported.[1,2] All were prepared through the same three-step approach including the classic Hantzsch pyridine synthesis using 2-nitrofuran-3-carbaldehyde, methyl acetoacetate and ammonia, further aromatization of the dihydropyridine obtained and, finally, reduction of the nitro group accompanied by intramolecular interaction of the amino group formed with the suitably situated ester. The method is limited, first of all, by the single applicable furancarbaldehyde and secondly, by the Hantzsch synthesis restrictions.

Over recent years so-called domino reactions have got an increasing importance in condensed heterocyclic chemistry,[3–7] since they allow creation of two or more rings at once at the expense of sequential chemical transformations, induced one by another. Recently the domino principle based approaches were applied by us and other researchers to preparation of pyrrolo- and thieno[2,3-*c*]-2,7-naphthyridines, respectively.[8,9] Continuing the investigations in the field it would be interesting to elaborate a domino synthesis of the corresponding furo analogues as an alternative to the known stepwise procedure.[1,2]

2. Results and discussion

Malonodinitrile and ethyl cyanoacetate were reported to react with epoxides yielding aminofurans **1**[10–15] (Fig. 1). When propenetricarbonitrile **2** (malonodinitrile dimer) was used as starting material the intermediate furans of type **1** (X is $C(NH_2)=C(CN)_2$) underwent further intramolecular addition of the amino group to the nitrile resulting in furopyridines **3**.[16] Thus, compounds **3** were obtained by formation of the two rings at once via the domino sequence including methylene alkylation and consecutive intramolecular additions of hydroxy and amino groups to nitriles. Previously the readily available pyridines **4–6**

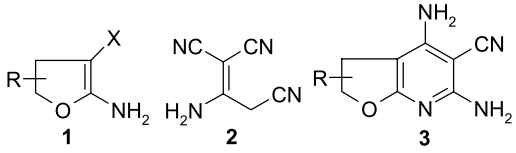

Figure 1. X=CN, CO_2Et.

Keywords: Domino reactions; Furo[2,3-*c*]-2,7-naphthyridines; Nitriles; Oxiranes; Spiro compounds.
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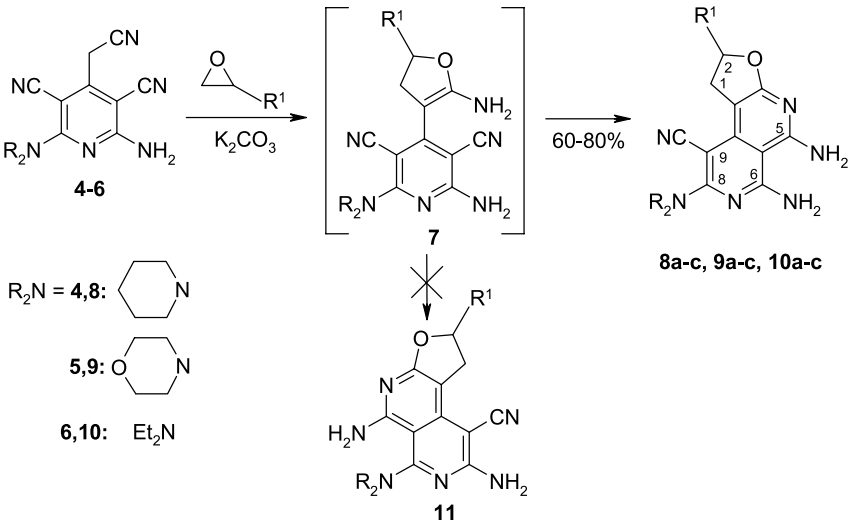


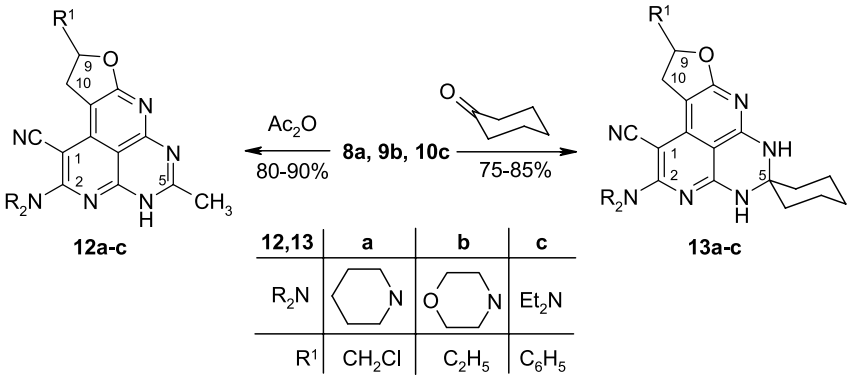
Scheme 1. R^1 = a: CH_2Cl, b: C_2H_5, c: C_6H_5.

were shown to be suitable precursors of various 2,7-naphthyridines.[8,17] Like compound **2** derivatives **4–6** contain the same vicinal CH_2CN groups moiety and CN and therefore, their reaction with epoxides should occur similarly and should afford the target furonaphthyridines. However, contrary to compound **2** there are two possibilities of a ring closure in the intermediates **7** (Scheme 1) with participation of 3-CN or 5-CN leading to the isomers **8–10** and **11**, respectively. Moreover different directions of the epoxide ring opening could not be excluded. Although in most cases oxiranes were reported to react with active methylenes from the less substituted side[10–16,18–23] a few examples of nucleophilic attack at the more substituted side[13,16,24–26] have also been noted. Hence the possible furan moiety isomerism in the products should be taken into consideration as well.

Nevertheless, treatment of the pyridines **4–6** with substituted oxiranes in ethanol in the presence of K_2CO_3 was found to give individual compounds isolated in 60–80% yields. ^1H and ^{13}C NMR spectra of isomeric 4- and 5-substituted furans **1** were well documented.[11–13] Comparison of the published data with the spectra of compounds obtained in the aliphatic region revealed their close resemblance with those of 5-substituted derivatives **1**. Hence the prepared compounds were assumed to be 2-substituted furonaphthyridines **8–10** or **11**, but not the 1-substituted isomers. Additional chemical transformations were used to distinguish the structures **8–10** and **11**. Thus, the selected derivatives **8a**, **9b**, **10c** were treated with acetic anhydride and cyclohexanone (Scheme 2). Both reactions resulted in a ring annulation and afforded fused heterocycles **12** and spirocyclic compound **13**. The similar transformations are well known for 1,8-naphthalenediamines[27–31] and have also been reported for certain 2,7-naphthyridine-1,8-diamines.[8,32] So the synthesis of derivatives **12**,**13** establishes the neighboring arrangement of the amino groups in the prepared furonaphthyridines thus excluding the structure **11**. Therefore the structures **8–10** should be assigned to the obtained compounds.

Of course, an X-ray crystallographic study would be desirable to determine the structures **8–10** undoubtedly. Unfortunately, we failed to grow a suitable crystal from the diamines **8–10**, but it was obtained from the cyclohexylidene derivative **13b**. An X-ray study confirmed its structure (Fig. 2) and therefore, proved the structure of the diamine precursors **8–10** unambiguously.

It should be emphasized that there were no detectable amounts of isomers in the reaction mixtures during synthesis of **8–10**. Hence the reaction occurs selectively both on the steps of epoxide ring cleavage and the amino group addition to nitrile. Considering the literature



Scheme 2.

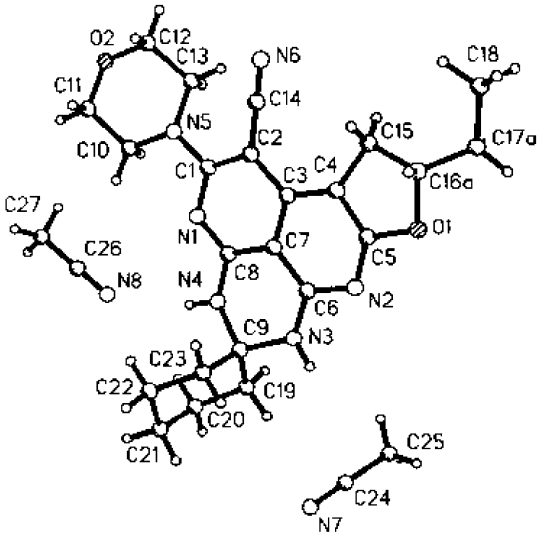


Figure 2. X-ray molecular structure of compound **13b** (a solvate with two molecules of acetonitrile) with the atom numbering used in the crystallographic analysis. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 270785. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

data[10–16,18–23] the selectivity of the oxiranes opening is expected. Additional steric hindrances at the active methylene of the pyridines **4–6** produced by neighboring nitriles seem only to uphold the selectivity. Predominant reactivity of 3-CN versus 5-CN in the pyridines **4–6** and related compounds was described earlier.[8,17,32] Its reasons were discussed in detail in our previous work[8] and are believed to be the same in the present case. Also it is interesting to note that the epichlorohydrine reacted clearly as epoxide saving the chloromethyl group and yielding furonaphthyridines **8a**,**9a**,**10a**. According to the literature both its reactions with active methylenes with and without participation of the chlorine are known.[16,33] Furthermore, it should be stated that derivatives **12**,**13** are the representatives of hitherto unknown heterocyclic systems, namely furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine and spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}.

To resume, present investigations has resulted in a simple and convenient synthesis of furo[2,3-*c*]-2,7-naphthyridine derivatives **8–10** based on the domino principle. Moreover, the derivatives of two novel heterocyclic frameworks **12**,**13** have been obtained by further ring annulations to the compounds **8–10**. The starting pyridines **4–6** are available in quantitative yields by reaction of 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile with appropriate secondary amines.[17] The chloropyridine precursor, in turn, was prepared from malonodinitrile and inorganic reagents in two steps.[32] Hence, the furonaphthyridines **8–10** and their condensed derivatives **12**,**13** have been synthesized from malonodinitrile in four and five steps, respectively. Other reagents used, for example, epoxides, acetic anhydride and cyclohexanone are also of general access. So the new heterocycles **8–10**,**12**,**13** of high complexity degree have been obtained, in fact, from simplest and cheapest sources through the sequence of moderate length. This exhibits a power and effectiveness of the domino strategy in heterocyclic synthesis. Apparently, the present method extends considerably the scope of furonaphthyridines chemistry and has significant advantages in comparison with the stepwise approach described.[1,2]

3. Experimental

The pyridines **4–6** were prepared as reported.[17] Other reagents were commercially available and were used without additional purification. Ethanol was dried with CaO. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. J values are in Hz. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

3.1. Furo[2,3-*c*]-2,7-naphthyridines 8–10. General procedure

Powdered K_2CO_3 (0.41 g, 3 mmol) was added to a solution of pyridine **4–6** (3 mmol) and corresponding epoxide (3 mmol) in ethanol (5 mL). The resulting mixture was refluxed for 1 h. After cooling the precipitate formed was filtered and thoroughly washed with water to remove inorganic materials. Recrystallization from an appropriate solvent afforded compounds **8–10**.

3.1.1. 5,6-Diamino-2-chloromethyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8a). Yield 71%. Mp 294–296 °C (from dioxane); δ_H 1.56–1.61 (6H, m, NR_2), 3.19 (1H, dd, $J^3=6.8$ Hz, $J^2=15.6$ Hz, 1-H), 3.54 (1H, dd, $J^3=9.6$ Hz, $J^2=15.6$ Hz, 1-H), 3.65 (4H, m, NR_2), 3.87 (1H, dd, $J^3=4.8$ Hz, $J^2=11.6$ Hz, CH_2Cl), 3.96 (1H, dd, $J^3=4.0$ Hz, $J^2=11.6$ Hz, CH_2Cl), 5.03 (1H, m, 2H), 6.46 (2H, s, NH_2), 7.10 (2H, s, NH_2). δ_C 24.5 (4-C_{NR2}), 26.2 (3,5-C_{NR2}), 31.3 (1-C), 47.8 (CH_2Cl), 48.8 (2,6-C_{NR2}), 68.1 (9-C), 79.7 (2-C), 92.5 (5a-C), 94.1 (9b-C), 121.2 (CN), 145.9 (9a-C), 159.4 (5-C), 159.8 (6-C), 162.3 (8-C), 167.4 (3a-C). Found: 56.78% C, 5.42% H, 9.80% Cl, 23.34% N; $C_{17}H_{19}ClN_6O$ requires 56.90% C, 5.34% H, 9.88% Cl, 23.42% N.

3.1.2. 5,6-Diamino-2-ethyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8b). Yield 81%. Mp 191–192 °C (from EtOH); δ_H 1.03 (3H, t, $J=7.2$, CH_3), 1.66 (6H, m, NR_2), 1.74 (2H, m, CH_2CH_3), 3.02 (1H, dd, $J^3=6.4$ Hz, $J^2=15.2$ Hz, 1-H), 3.54 (1H, dd, $J^3=10.0$ Hz, $J^2=15.2$ Hz, 1-H), 3.66 (4H, m, NR_2), 4.68 (1H, m, 2-H), 6.12 (2H, s, NH_2), 6.69 (2H, s, NH_2). δ_C 9.0 (CH_3), 24.1 (3,5-C_{NR2}), 25.2 (4-C_{NR2}), 27.3 (CH_2CH_3), 34.9 (1-C), 47.1 (2,6-C_{NR2}), 66.4 (9-C), 82.3 (2-C), 89.5 (5a-C), 92.1 (9b-C), 121.8 (CN), 146.0 (9a-C), 157.3 (6-C), 160.7 (5-C), 164.2 (8-C), 168.5 (3a-C). Found: 63.97% C, 6.53% H, 24.82% N; $C_{18}H_{22}N_6O$ requires 63.89% C, 6.55% H, 24.83% N.

3.1.3. 5,6-Diamino-2-phenyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8c). Yield 62%. Mp 206–207 °C (from acetonitrile); δ_H 1.42

(2H, m, NR_2), 1.54 (4H, m, NR_2), 3.48 (4H, m, NR_2), 4.30 (1H, dd, $J^3=1.4$ Hz, $J^2=8.8$ Hz, 1-H), 4.79 (1H, dd, $J^3=8.4$ Hz, $J^2=8.8$ Hz, 1-H), 5.00 (1H, dd, $J^3=1.4$ Hz, $J^3=8.4$ Hz, 2-H), 6.63 (2H, s, NH_2), 7.02 (2H, d, $J=7.6$ Hz, 2,6-H_{Ph}), 7.14 (2H, s, NH_2), 7.17 (1H, t, $J=7.6$ Hz, 4-H_{Ph}), 7.25 (2H, t, $J=7.6$ Hz, 3,5-H_{Ph}). δ_C 24.1 (4-C_{NR2}), 25.7 (3,5-C_{NR2}), 44.3 (1-C), 48.3 (2,6-C_{NR2}), 67.8 (9-C), 77.4 (2-C), 92.2 (5a-C), 97.5 (9b-C), 120.2 (CN), 126.4 (4-C_{Ph}), 126.9 (3,5-C_{Ph}), 128.4 (2,6-C_{Ph}), 144.4 (1-C_{Ph}), 145.9 (9a-C), 159.2 (5-C), 160.0 (6-C), 161.9 (8-C), 168.4 (3a-C). Found: 68.50% C, 5.60% H, 21.80% N; $C_{22}H_{22}N_6O$ requires 68.38% C, 5.74% H, 21.75% N.

3.1.4. 5,6-Diamino-2-chloromethyl-8-(4-morpholinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9a). Yield 73%. Mp >300 °C (from DMF); δ_H 3.19 (1H, dd $J^3=6.8$ Hz, $J^2=16.0$ Hz, 1-H), 3.54 (1H, dd $J^3=9.6$ Hz, $J^2=16.0$ Hz, 1-H), 3.65 (8H, m, NR_2), 3.87 (1H, dd $J^3=4.4$ Hz, $J^2=11.2$ Hz, CH_2Cl), 3.95 (1H, dd $J^3=3.6$ Hz, $J^2=11.2$ Hz, CH_2Cl), 5.04 (1H, m, 2-H), 6.52 (2H, s, NH_2), 7.21 (2H, s, NH_2). δ_C 31.1 (1-C), 45.4 (CH_2Cl), 46.1 (NCH_2), 65.6 (OCH_2), 69.7 (9-C), 79.0 (2-C), 93.0 (5a-C), 94.1 (9b-C), 119.1 (CN), 145.4 (9a-C), 158.6 (6-C), 159.0 (5-C), 162.9 (8-C), 165.4 (3a-C). Found: 53.48% C, 4.67% H, 9.80% Cl, 23.34% N; $C_{16}H_{17}ClN_6O_2$ requires 53.26% C, 4.75% H, 9.83% Cl, 23.29% N.

3.1.5. 5,6-Diamino-2-ethyl-8-(4-morpholinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9b). Yield 77%. Mp 263–264 °C (from EtOH); δ_H 0.94 (3H, t, $J=7.4$ Hz, CH_3), 1.69 (2H, m, CH_2CH_3), 2.97 (1H, dd, $J^3=7.2$ Hz, $J^2=15.2$ Hz, 1-H), 3.51 (1H, dd, $J^3=9.6$ Hz, $J^2=15.2$ Hz, 1-H), 3.65 (8H, m, NR_2), 4.71 (1H, m, 2-H), 6.46 (2H, s, NH_2), 7.18 (2H, s, NH_2). δ_C 9.2 (CH_3), 28.7 (CH_2CH_3), 32.6 (1-C), 48.0 (NCH_2), 66.2 (OCH_2), 68.6 (9-C), 82.3 (2-C), 92.1 (5a-C), 94.4 (9b-C), 120.7 (CN), 145.3 (9a-C), 159.2 (5-C), 159.6 (6-C), 162.3 (8-C), 167.5 (3a-C). Found: 59.95% C, 5.96% H, 24.92% N; $C_{17}H_{20}N_6O_2$ requires 59.99% C, 5.92% H, 24.69% N.

3.1.6. 5,6-Diamino-8-(4-morpholinyl)-2-phenyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9c). Yield 65%. Mp 242–243 °C (from dioxane); δ_H 3.57 (8H, m, NR_2), 4.28 (1H, dd, $J^3=1.6$ Hz, $J^2=10.4$ Hz, 1-H), 4.79 (1H, dd, $J^3=8.8$ Hz, $J^2=10.4$ Hz, 1-H), 5.00 (1H, dd, $J^3=8.8$,1.6 Hz, 2-H), 7.02 (2H, d, $J=7.6$ Hz, 2,6-H_{Ph}), 7.13 (2H, s, NH_2), 7.17 (3H, m, NH_2, 4-H_{Ph}), 7.25 (2H, dd, $J=7.6$, 7.6 Hz, 3,5-H_{Ph}). δ_C 43.7 (1-C), 49.0 (NCH_2), 64.9 (OCH_2), 65.0 (9-C), 78.2 (2-C), 92.4 (5a-C), 97.0 (9b-C), 120.7 (CN), 124.3 (3,5-C_{Ph}), 125.6 (4-C_{Ph}), 128.0 (2,6-C_{Ph}), 144.7 (1-C_{Ph}), 147.6 (9a-C), 160.6 (5-C), 161.0 (6-C), 162.3 (8-C), 169.9 (3a-C). Found: 64.65% C, 5.14% H, 21.66% N; $C_{21}H_{20}N_6O_2$ requires 64.94% C, 5.19% H, 21.64% N.

3.1.7. 5,6-Diamino-2-chloromethyl-8-diethylamino-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10a). Yield 76%. Mp 300–301 °C (from dioxane); δ_H 1.23 (6H, t, $J=6.0$ Hz, $2CH_3$), 3.29 (1H, dd, $J^3=6.4$ Hz, $J^2=15.6$ Hz, 1-H), 3.63 (5H, m, NCH_2, 1-H), 3.77 (1H, dd $J^3=4.4$ Hz, $J^2=10.8$ Hz, CH_2Cl), 3.83 (1H, dd $J^3=3.2$ Hz, $J^2=10.8$ Hz, CH_2Cl), 4.97 (1H, m, 2-H), 6.17 (2H, s, NH_2), 6.64 (2H, s, NH_2). δ_C 13.6 (CH_3), 31.2 (1-C), 43.2 (NCH_2), 47.5 (CH_2Cl), 65.8 (9-C), 79.1 (2-C), 91.8 (5a-C), 93.7 (9b-C), 121.2 (CN), 145.9 (9a-C), 158.8 (5-C), 159.3 (6-C), 160.1 (8-C), 167.1 (3a-C). Found: 55.34% C, 5.60% H, 10.43% Cl, 24.17 N; $C_{16}H_{19}ClN_6O$ requires 55.41% C, 5.52% H, 10.22% Cl, 24.23 N.

3.1.8. 5,6-Diamino-8-diethylamino-2-ethyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10b). Yield 83%. Mp 212–213 °C (from *i*-PrOH); δ_H 1.03 (3H, t, $J=7.4$ Hz, CH_3), 1.23 (6H, t, $J=6.8$ Hz, $2CH_3$), 1.74 (2H, m, CH_2CH_3), 3.05 (1H, dd, $J^3=6.8$ Hz, $J^2=15.2$ Hz, 1-H), 3.57 (1H, dd, $J^3=9.6$ Hz, $J=15.2$, 1-H), 3.63 (4H, q, $J=6.8$ Hz, NCH_2), 4.66 (1H, m, 2-H), 6.07 (2H, s, NH_2), 6.59 (2H, s, NH_2). δ_C 9.5 (CH_2CH_3), 13.8 (CH_3), 27.3 (CH_2CH_3), 33.0 (1-C), 44.0 (NCH_2), 65.9 (9-C), 82.6 (2-C), 93.7 (9b-C), 94.6 (5a-C), 120.1 (CN), 142.9 (9a-C), 158.4 (5-C), 162.2 (6-C), 162.4 (8-C), 167.0 (3a-C). Found: 62.40% C, 6.76% H, 25.83% N; $C_{17}H_{22}N_6O$ requires 62.56% C, 6.79% H, 25.75% N.

3.1.9. 5,6-Diamino-8-diethylamino-2-phenyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10c). Yield 79%. Mp 170–171 °C (from dioxane); δ_H 1.11 (6H, t, $J=7.0$ Hz, $2CH_3$), 3.48 (4H, m, NCH_2), 4.33 (1H, dd, $J^3=2.0$ Hz, $J^2=8.4$ Hz, 1-H), 4.78 (1H, dd, $J^3=8.8$ Hz, $J^2=8.4$ Hz, 1-H), 5.09 (1H, dd, $J^3=8.8$, 2.0 Hz, 2-H), 6.34 (2H, s, NH_2), 6.61 (2H, s, NH_2), 7.08–7.14 (3H, m, 2,6,4-H_{Ph}), 7.22 (2H, dd, $J=7.6$, 7.6 Hz, 3,5-H_{Ph}). δ_C 16.7 (CH_3), 43.4 (NCH_2), 44.9 (1-C), 67.1 (9-C), 78.6 (2-C), 93.0 (5a-C), 98.3 (9b-C), 119.7 (CN), 126.9 (2,6-C_{Ph}), 127.1 (4-C_{Ph}), 127.2 (3,5-C_{Ph}), 146.5 (9a-C), 146.8 (1-C_{Ph}), 158.1 (5-C), 161.4 (6-C), 164.4 (8-C), 168.3 (3a-C). Found: 67.57% C, 5.81% H, 22.48% N; $C_{21}H_{22}N_6O$ requires 67.36% C, 5.92% H, 22.44% N.

3.2. Furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridines 12a–c. General procedure

A solution of the diamine **8a**,**9b**,**10c** (2.5 mmol) in acetic anhydride (3 mL) was heated at 100–110 °C for 1 h. After cooling the precipitated solid was filtered, washed with water and recrystallized from DMF to give derivatives **12a**–**c**.

3.2.1. 9-Chloromethyl-5-methyl-2-(1-piperidinyl)-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12a). Yield 92%. Mp >300 °C (from DMF); δ_H 1.63 (6H, m, NR_2), 2.36 (3H, s, 5-CH_3), 3.22 (1H, dd $J^3=7.2$ Hz, $J^2=16.0$ Hz, 10-H), 3.57 (1H, dd $J^3=9.6$ Hz, $J^2=16.0$ Hz, 10-H), 3.70 (4H, m, NR_2), 3.95 (1H, dd $J^3=4.8$ Hz, $J^2=11.6$ Hz, CH_2Cl), 4.03 (1H, dd $J^3=4.0$ Hz, $J^2=11.6$ Hz, CH_2Cl), 5.15 (1H, m, 9-H), 12.84 (1H, br s, NH). δ_C 24.6 (5-CH_3), 24.7 (4-C_{NR2}), 27.8 (3,5-C_{NR2}), 32.6 (10-C), 46.3 (CH_2Cl), 47.8 (2,6-C_{NR2}), 74.6 (1-C), 86.1 (9-C), 103.0 (10a-C), 110.0 (10c-C), 121.1 (CN), 149.6 (10b-C), 151.7 (6a-C), 156.1 (3a-C), 162.8 (2-C), 168.0 (5-C), 168.7 (7a-C). Found: 59.81% C, 5.10% H, 9.39% Cl, 21.92% N; $C_{19}H_{19}ClN_6O$ requires 59.61% C, 5.00% H, 9.26% Cl, 21.95% N.

3.2.2. 9-Ethyl-5-methyl-2-(4-morpholinyl)-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12b). Yield 81%. Mp >300 °C (from DMF); δ_H 0.97 (3H, t, $J=7.2$ Hz, CH_2CH_3), 1.75 (2H, m,

CH_2CH_3), 2.36 (3H, s, 5-CH_3), 2.97 (1H, dd, $J^3=8.0$ Hz, $J^2=16.4$ Hz, 10-H), 3.49 (1H, dd, $J^3=9.2$ Hz, $J^2=16.4$ Hz, 10-H), 3.69 (8H, m, NR_2), 4.80 (1H, m, 9-H), 13.11 (1H, br s, NH). δ_C 9.9 (CH_2CH_3), 22.9 (5-CH_3), 31.1 (CH_2CH_3), 33.9 (10-C), 51.7 (NCH_2), 69.0 (OCH_2), 76.4 (1-C), 94.1 (9-C), 104.2 (10a-C), 108.7 (10c-C), 118.2 (CN), 147.1 (10b-C), 153.8 (6a-C), 156.3 (3a-C), 163.0 (2-C), 168.2 (5-C), 168.7 (7a-C). Found: 62.74% C, 5.40% H, 22.94% N; $C_{19}H_{20}N_6O_2$ requires 62.62% C, 5.53% H, 23.06% N.

3.2.3. 2-Diethylamino-5-methyl-9-phenyl-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12c). Yield 93%. Mp >300 °C (from DMF); δ_H 1.12 (6H, t, $J=6.8$ Hz, $2CH_3$), 2.41 (3H, s, 5-CH_3), 3.56 (4H, m, NCH_2), 4.39 (1H, dd, $J^3=1.2$ Hz, $J^2=8.8$ Hz, 10-H), 4.93 (1H, dd, $J^3=8.4$ Hz, $J^2=8.8$ Hz, 10-H), 5.10 (1H, dd, $J^3=8.4$ Hz, 1.2,-H), 7.08 (2H, d, $J=8.0$ Hz, 2,6-H_{Ph}), 7.21 (1H, t, $J=8.0$ Hz, 4-H_{Ph}), 7.29 (2H, dd, $J=8.0$, 8.0 Hz, 3,5-H_{Ph}), 12.51 (1H, s, NH). δ_C 13.8 (CH_3), 24.4 (5-CH_3), 44.9 (10-C), 45.3 (NCH_2), 77.0 (1-C), 89.1 (9-C), 104.8 (10a-C), 108.9 (10c-C), 116.7 (CN), 127.1 (3,5-C_{Ph}), 128.0 (2,6-C_{Ph}), 128.9 (4-C_{Ph}), 142.9 (1-C_{Ph}), 145.3 (10b-C), 152.6 (6a-C), 156.0 (3a-C), 164.3 (2-C), 166.7 (5-C), 168.0 (7a-C). Found: 69.37% C, 5.35% H, 21.19% N; $C_{23}H_{22}N_6O$ requires 69.33% C, 5.57% H, 21.09% N.

3.3. Spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexanes} 13a–c. General procedure

A solution of the diamine **8a**,**9b**,**10c** (2.5 mmol) in cyclohexanone (3 mL) was heated at 100 °C for 2 h. After cooling it was diluted with water resulting in a brown oil separation. The liquid was decanted and the oil was dissolved in ethanol (10 mL). Water (10 mL) was added to ethanolic solution and a pale solid precipitated. It was filtered and recrystallized from DMF–H_2O (1:1 v/v) mixture yielding compounds **13a–c**. During the recrystallization, a long heating time should be avoided.

3.3.1. 9-Chloromethyl-2-(1-piperidinyl)-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13a). Yield 82%. Mp 186–187 °C (from aqueous DMF); δ_H 1.36 (1H, m, 4′-H), 1.46 (1H, m, 4′-H), 1.68 (12H, m, NR_2, 2′,3′,5′,6′-H), 1.82 (2H, m, 2′,6′-H), 3.20 (1H, dd, $J^3=6.8$ Hz, $J^2=16.0$ Hz 10-H), 3.52 (1H, dd, $J^3=9.6$ Hz, $J^2=16.0$ Hz 10-H), 3.66 (4H, m, NR_2), 3.78 (1H, dd, $J^3=5.2$ Hz, $J^2=11.2$ Hz, CH_2Cl), 3.84 (1H, dd, $J^3=5.2$ Hz, $J^2=11.2$ Hz, CH_2Cl), 4.98 (1H, m, 9-H), 7.58 (1H, s, NH), 7.60 (1H, s, NH). δ_C 20.9 (3′,5′-C), 24.6 (4′-C), 25.1 (4-C_{NR2}), 26.3 (3,5-C_{NR2}), 30.6 (10-C), 37.3 (2′,6′-C), 47.7 (CH_2Cl), 49.4 (2,6-C_{NR2}), 68.5 (1-C), 68.7 (5-C), 79.9 (9-C), 89.8 (10c-C), 93.3 (10a-C), 121.0 (CN), 143.7 (10b-C), 156.0 (6a-C), 156.2 (3a-C), 164.5 (2-C), 169.5 (7a-C). Found: 62.76% C, 6.13% H, 8.10% Cl, 19.30% N; $C_{23}H_{27}ClN_6O$ requires 62.93% C, 6.20% H, 8.08% Cl, 19.15% N.

3.3.2. 9-Ethyl-2-(4-morpholinyl)-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13b). Yield 76%. Mp 237 °C (from aqueous DMF); δ_H 1.04 (1H, t, $J=7.2$ Hz, CH_3), 1.36 (1H, m, 4′-H), 1.47 (1H, m, 4′-H), 1.61–1.82 (10H, m, CH_2CH_3, 2′,3′,5′,6′-H), 2.96 (1H, dd, $J^3=8.0$ Hz, $J^2=14.8$ Hz, 10-H), 3.48 (1H, dd, $J^3=9.6$ Hz, $J^2=14.8$ Hz, 10-H), 3.65 (4H, m, NR_2), 3.71 (4H, m, NR_2), 4.68 (1H, m, 9-H), 7.57 (1H, s, NH), 7.61 (1H, s, NH). δ_C 9.4 (CH_2CH_3), 22.7 (3′,5′-C), 22.8 (4′-C), 31.3 (10-C), 33.2 (CH_2CH_3), 36.2 (2′,6′-C), 46.5 (NCH_2), 67.6 (1-C), 68.0 (5-C), 68.6 (OCH_2), 82.8 (9-C), 88.5 (10c-C), 92.3 (10a-C), 118.9 (CN), 142.7 (10b-C), 154.1 (6a-C), 155.5 (3a-C), 163.7 (2-C), 167.8 (7a-C). Found: 65.60% C, 6.63% H, 19.83% N; $C_{23}H_{28}N_6O_2$ requires 65.69% C, 6.71% H, 19.98% N.

3.3.3. 2-Diethylamino-9-phenyl-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13c). Yield 87%. Mp 198–199 °C (from aqueous DMF); δ_H 1.06 (6H, t, $J=7.0$ Hz, $2CH_3$), 1.28 (1H, m, 4′-H), 1.40 (1H, m, 4′-H), 1.63–1.80 (8H, m, 2′,3′,5′,6′-H), 3.49 (4H, q, $J=7.0$ Hz, NCH_2), 4.28 (1H, dd, $J^3=2.0$ Hz, $J^2=8.8$ Hz, 10-H), 4.80 (1H, dd, $J^3=9.2$ Hz, $J^2=8.8$ Hz, 10-H), 4.97 (1H, dd, $J^3=2.0$, 9.2 Hz, 9-H), 7.04 (2H, d, $J=7.2$ Hz, 2,6-H_{Ph}), 7.17 (1H, t, $J=7.2$ Hz, 4-H_{Ph}), 7.26 (2H, t, $J=7.2$ Hz, 3,5-H_{Ph}), 7.88 (2H, s, 2NH). δ_C 13.6 (CH_3), 18.7 (3′,5′-C), 23.5 (4′-C), 37.8 (2′,6′-C), 43.7 (10-C), 43.9 (NCH_2), 68.0 (1-C), 68.5 (5-C), 88.5 (10c-C), 89.1 (9-C), 91.5 (10a-C), 119.7 (CN), 125.2 (4-C_{Ph}), 127.2 (3,5-C_{Ph}), 130.8 (2,6-C_{Ph}), 141.2 (10b-C), 144.6 (1-C_{Ph}), 155.1 (6a-C), 159.5 (3a-C), 163.9 (2-C), 167.7 (7a-C). Found: 71.20% C, 6.51% H, 18.27% N; $C_{27}H_{30}N_6O$ requires 71.34% C, 6.65% H, 18.49% N.

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