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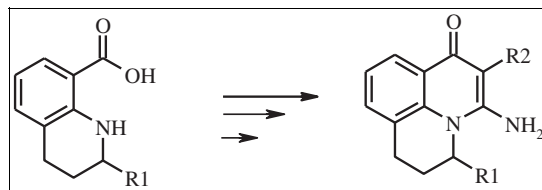
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A simple and efficient method is developed. Novel 2-amino-4-quinolone derivatives are synthesized. The products that have several functional groups for possible future modifications are described.

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INTRODUCTION

The interest in synthesis of enamino-ketones series based on quinoline core is explained by the fact that these compounds have multiple reaction sites and can serve as precursors for the synthesis of new heterocyclic systems, 2-aminoquinolone can easily be converted to 4-hydroxyquinolone-2, which are used as a diuretic [1]. Also, amino group in their system conjugate with keto group; that is why, it is like the amide group in these systems. That is why, it could serve as an isosteric analogue of amide group. Recent publication of Erb and coworkers showed that 2-amino-4-quinolones could be a potential potassium channel openers [2]. The system of benzo[e,f]quinolizine is a structural component of Lycopodium alkaloids, which show pronounced stimulatory effect on the respiratory center, as well as increased blood pressure [3].

RESULTS AND DISCUSSION

There are many methods for synthesis of 4-quinolones, we used one of them. It is based on the interaction of *N*-methylanthranilate and arylacetonitriles [4] in the basic case. This route permits the synthesis of a condensed system with desired substitutes in aromatic ring and in system of 4-quinolone. We started from 1,2,3,4-tetrahydroquinoline-8-carboxylic acid methyl ester to 2-methyl-1,2,3,4-tetrahydroquinoline-8-carboxylic acid ethyl ester (Scheme 1).

The synthesis of 1,2,3,4-tetrahydroquinoline-8-carboxylic acid in two alternative routes is described in literature (Scheme 2). Synthesis is possible either from the corresponding isatin [5] or from quinoline-8-carboxylic acid [6],[7]. The path through the isatin was described for acid with substituent in C-2 position. We used Raney nickel for reduction of both acids [8].

For starting, quinoline-8-carboxylic acid was used a modified method [9]. As oxidant, we used iodine in the Skraup's reaction. Esters were obtained by standard methods using thionylchloride and the corresponding absolute alcohol.

The 4-quinolones were formed when esters were heated with arylacetonitriles with *t*-BuONa in pyridine.

In IR, there are absorption bands of the synthesized compounds, the primary amino groups (3440 and 3340 cm^{-1}), and conjugations keto-group (1505–1512 cm^{-1} , depending of the substituent). The amino group's signal is observed as two-proton singlet (exchangeable with D_2O) at 5.6–6.9 ppm in ^1H NMR.

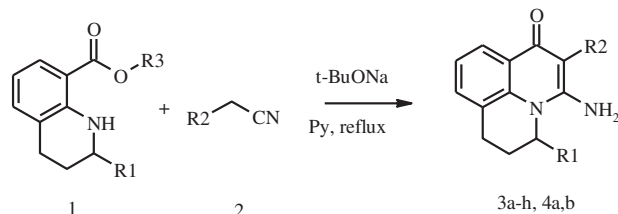
In summary, we describe the products that have several functional groups for possible future modifications. The structure of the synthesized compounds was proved by methods of NMR, IR spectroscopy, and elemental analysis.

EXPERIMENTAL

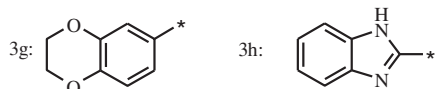
General data. Solvents were purified according to standard methods [10]. All commercially available chemicals were purchased from Aldrich and Merck. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Gemini spectrometer, using $\text{DMSO}-d_6$. All chemical shifts are reported in ppm relative to TMS. IR spectra were recorded on spectrometer Nicolet Nexus 470 in tablets KBr. Mass spectra were recorded on a VG micromass 7070H spectrometer in chemical ionization mode (atmospheric pressure chemical ionisation). Melting points were determined through a Fisher–Johns apparatus and are uncorrected. Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer.

8-Quinolonecarboxylic acid (5a). Anthranilic acid, 54.8 g (0.4 mol), was dissolved in 140-mL 80% H_2SO_4 . The reaction mixture was heated with stirring until 140°, then added a catalytic amount of NaI and added dropwise 35.8 mL

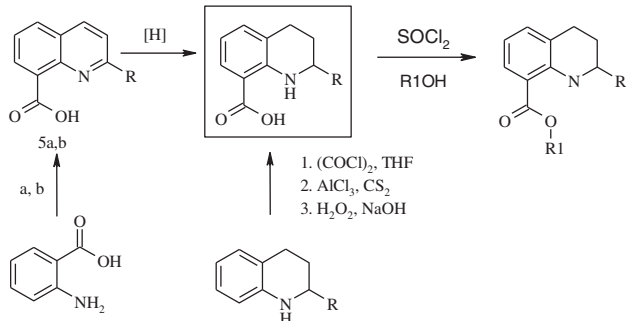
Scheme 1. Synthesis of 2-amino-4-quinolones derivatives.



R1=H (3a-h), R3=Me; R1= Me (4a, 4b), R3=Et

R2= 3a, 4a: C₆H₅-, 3b: 4-FC₆H₄-3c: 3-ClC₆H₄-, 3d, 4b: 3-CF₃C₆H₄-3e: 4-MeOC₆H₄-, 3f: 3,4-(MeO)₂C₆H₃-

Scheme 2. Two alternative routes for synthesis of 1,2,3,4-tetrahydroquinoline-8-carboxylic acids and their esters.



R= H, Me

a: R=H, glycerole, H₂SO₄, NaI, 5a

b: R=Me, crotonic aldehyde, HCl, 5b

R1=Me (6a), Et (6b)

(0.486 mol) of glycerol, maintaining a constant temperature. The mixture was heated at this temperature for 6.5 h, cooled to room temperature and neutralized with an alkali, and the precipitate was filtered. The product was purified by recrystallization from ethanol. Yield 60%, mp 186–188°C (literature 183–185°C).

Synthesis of esters of 1,2,3,4-tetrahydroquinoline-8-carboxylic acids (6a,b). To a 0.02 mole of the corresponding acid, that dissolved in absolute alcohol, was added dropwise 0.035 mol SOCl₂. Then, mixture was boiled for 2–3 days, concentrated under reduced pressure, added with a small amount of water, and neutralized with NaHCO₃. The ester was extracted with toluene and dried over Na₂SO₄. Solvent was distilled away. Boiling point = 99°C/0.06 mmHg. (not substituted), 102°C/0.06 mmHg (with methyl in the 2-position).

General method for the synthesis of 3-amino-2-aryl-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-1-quinolinones (3a–h, 4a,b). Ester, 3.5 mmol, was mixed with 3.5 mmol farylacetonitrile, added with 5 mL of dry pyridine, and 4.1 mmol *t*-BuONa, after which the mixture was heated for 6 h. The solvent was evaporated, and the residue was dissolved in a little water and neutralized with hydrochloric acid. The precipitate was filtered, washed with water, and crystallized from 2-propanol

3-Amino-2-phenyl-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3a). This compound was obtained as white powder.

Yield: 80%; mp 287–288°C; ¹H NMR (400.4 MHz, DMSO-*d*₆): 2.17 (2H, m), 2.98 (2H, t, *J* = 6 Hz), 4.01 (2H, t, *J* = 5.6 Hz), 5.67 (2H, s), 7.06 (1H, t, *J* = 7.6 Hz), 7.2 (5H, m), 7.4 (1H, t, *J* = 7.2 Hz), 7.94 (1H, d, *J* = 7.6 Hz).

¹³C NMR (100.7 MHz, DMSO-*d*₆): 21.33; 27.1; 45.5; 104.37; 121.74; 124.10; 125.29; 126.48; 126.90; 128.94; 130.12; 132.13; 136.16; 136.37; 152.89; 171.87, IR (KBr) ν: 3428, 3303, 1647, 1600, 1524 cm⁻¹; MS: *m/z* 277 (M⁺); *Anal.* Calcd for C₁₈H₁₆N₂O: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.19; H, 5.79; N, 10.11.

3-Amino-2-(4-fluorophenyl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3b). This compound was obtained as white powder.

Yield: 85%; mp 283–284°C; ¹H NMR (400.4 MHz, DMSO-*d*₆): 2.15 (2H, m), 2.96 (2H, t, *J* = 5.6 Hz), 4.0 (2H, t, *J* = 6 Hz), 5.74 (2H, s), 6.95 (2H, d, *J* = 8.8 Hz), 7.06 (1H, t, *J* = 7.6 Hz), 7.14 (2H, d, *J* = 8.4 Hz), 7.26 (1H, m), 7.92 (1H, d, *J* = 7.6 Hz).

¹³C NMR (100.7 MHz, DMSO-*d*₆): 21.32; 27.10; 45.51; 103.24; 115.60; 115.76; 121.74; 124.06; 125.17; 126.48; 130.15; 132.53; 134.07; 134.14; 136.18; 152.44; 160.49; 171.89, IR (KBr) ν: 3445, 3310, 1647, 1611, 1523 cm⁻¹; MS: *m/z* 295 (M⁺); *Anal.* Calcd for C₁₈H₁₅FN₂O: C, 73.45; H, 5.14; N, 9.52. Found: C, 73.39; H, 5.08; N, 9.47.

3-Amino-2-(3-chlorophenyl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3c). This compound was obtained as white powder.

Yield: 67%; mp 277–278°C; ¹H NMR (400.4 MHz, DMSO-*d*₆): 2.15 (2H, m), 2.96 (2H, t, *J* = 5.2 Hz), 3.99 (2H, t, *J* = 5.2 Hz), 5.9 (2H, s), 7.07 (1H, d, *J* = 8.8 Hz), 7.2 (1H, d, *J* = 7.6 Hz), 7.27 (3H, m), 7.4 (1H, t, *J* = 7.2 Hz), 7.92 (1H, d, *J* = 7.6 Hz).

¹³C NMR (100.7 MHz, DMSO-*d*₆): 22.8; 27.3; 45.8; 97; 113.9; 117; 123.7; 126.5; 127; 127.1; 128; 130; 133.7; 134.1; 137.1; 142.5; 156.8; 175.4, IR (KBr) ν: 3446, 3324, 1644, 1611, 1518 cm⁻¹; MS: *m/z* 311 (M⁺); *Anal.* Calcd for C₁₈H₁₅ClN₂O: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.51; H, 4.81; N, 8.99.

3-Amino-2-(3-trifluoromethylphenyl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3d). This compound was obtained as white powder.

Yield: 90%; mp 231–232°C; ¹H NMR (400.4 MHz, DMSO-*d*₆): 2.2 (2H, m), 3.03 (2H, m), 4.1 (2H, m), 6.9 (2H, s), 7.23 (1H, t, *J* = 8 Hz), 7.43 (1H, d, *J* = 6.8 Hz), 7.57 (2H, m), 7.67 (2H, m), 8.06 (1H, d, *J* = 8 Hz).

¹³C NMR (100.7 MHz, DMSO-*d*₆): 20.97; 26.76; 46.67; 104.8; 118.52; 121.46; 123.15; 123.44; 124.93; 125.97; 127.23; 128.81; 130.45; 131.43; 134.62; 135.72; 136.15; 153.82; 171.82, IR (KBr) ν: 3465, 3279, 1637, 1617, 1518 cm⁻¹; MS: *m/z* 345 (M⁺); *Anal.* Calcd for C₁₉H₁₅F₃N₂O: C, 66.28; H, 4.39; N, 8.14. Found: C, 66.21; H, 4.35; N, 8.11.

3-Amino-2-(4-methoxyphenyl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3e). This compound was obtained as white powder.

Yield: 75%; mp 279–280°C; ¹H NMR (400.4 MHz, DMSO-*d*₆): 2.17 (2H, m), 2.97 (2H, t, *J* = 5.6 Hz), 3.82 (3H, s), 4.0 (2H, t, *J* = 6 Hz), 5.71 (2H, s), 6.95 (2H, d, *J* = 8.8 Hz), 7.06 (1H, t, *J* = 7.6 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 7.26 (1H, d, *J* = 6.8 Hz), 7.93 (1H, d, *J* = 7.2 Hz).

¹³C NMR (100.7 MHz, DMSO-*d*₆): 21.32; 27.1; 45.55; 55.51; 104.02; 114.52; 121.72; 124.05; 125.07; 126.44; 128.13; 130.06,

133.14, 136.07, 152.55, 158.38, 171.73. IR (KBr) ν : 3428, 3330, 1653, 1626, 1516 cm^{-1} ; MS: m/z 307 (M^+); *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.41; H, 5.86; N, 9.11.

3-Amino-2-(3,4-dimethoxyphenyl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3f). This compound was obtained as white powder.

Yield: 70%; mp 269–270°C; ^1H NMR (400.4 MHz, $\text{DMSO}-d_6$): 2.14 (2H, m), 2.96 (2H, t, $J=6$ Hz), 3.73 (3H, s), 3.8 (3H, s), 3.99 (2H, t, $J=5.6$ Hz), 5.71 (2H, s), 6.77 (2H, m), 6.94 (1H, d, $J=8$ Hz), 7.06 (1H, t, $J=7.2$ Hz), 7.25 (1H, d, $J=6.8$ Hz), 7.94 (1H, d, $J=7.6$ Hz).

^{13}C NMR (100.7 MHz, $\text{DMSO}-d_6$): 21.35, 27.12, 45.48, 55.89, 56.04, 104.29, 112.69, 115.96, 121.64, 124.11, 124.17, 126.38, 125.30, 128.75, 130.01, 136.10, 148.02, 149.29, 152.5, 171.95; IR (KBr) ν : 3450, 3329, 1654, 1627, 1516 cm^{-1} ; MS: m/z 337 (M^+); *Anal.* Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: C, 71.41; H, 5.99; N, 8.34. Found: C, 71.36; H, 5.95; N, 8.29.

3-Amino-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3g). This compound was obtained as white powder.

Yield: 65%; mp 258–259°C; ^1H NMR (400.4 MHz, $\text{DMSO}-d_6$): 2.1 (2H, m), 2.96 (2H, m), 3.99 (2H, t, $J=6$ Hz), 4.2 (4H, s), 5.7 (2H, s), 6.68 (2H, m), 6.84 (1H, d, $J=8$ Hz), 7.06 (1H, t, $J=8$ Hz), 7.25 (1H, d, $J=6.8$ Hz), 7.92 (1H, d, $J=8$ Hz).

^{13}C NMR (100.7 MHz, $\text{DMSO}-d_6$): 22.9, 27.4, 45.9, 64.2, 64.3, 97, 111.4, 112.6, 113.7, 117, 121.3, 123.6, 124.8, 127.1, 137.3, 142.7, 149.3, 149.8, 156.8, 175.5, IR (KBr) ν : 3429, 3329, 1646, 1612, 1518 cm^{-1} ; MS: m/z 335 (M^+); *Anal.* Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.77; H, 5.37; N, 8.30.

3-Amino-2-(1H-benzimidazol-2-yl)-6,7-dihydro-1H, 5H-pyrido [3,2,1-ij]-quinolin-1-on (3h). This compound was obtained as white powder.

Yield: 65%; mp more than 300°C; ^1H NMR (400.4 MHz, $\text{DMSO}-d_6$): 2.2 (2H, m), 2.98 (2H, t, $J=6$ Hz), 4.06 (2H, t, $J=5.2$ Hz), 7.11 (2H, m), 7.15 (1H, t, $J=7.6$ Hz), 7.33 (1H, d, $J=6.8$ Hz), 7.57 (2H, m), 8.15 (1H, d, $J=7.2$ Hz), 11.52 (1H, s), 13.72 (1H, s).

^{13}C NMR (100.7 MHz, $\text{DMSO}-d_6$): 21.12, 26.96, 45.20, 91.02, 96.08, 111.48, 117.09, 121.30, 122.12, 123.78, 124.43, 125.86, 130.79, 132.12, 135.13, 141.8, 153.11, 154.80, 173.23. IR (KBr) ν : 3448, 3280, 1643, 1541, 1523 cm^{-1} ; MS: m/z 317 (M^+); *Anal.* Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}$: C, 72.14; H, 5.10; N, 17.71. Found: C, 72.08; H, 5.04; N, 17.68.

3-Amino-5-methyl-2-phenyl-6,7-dihydro-1H, 5H-pyrido[3,2,1-ij]-quinolin-1-on (4a). This compound was obtained as white powder.

Yield: 67%; mp 150–151°C; ^1H NMR (400.4 MHz, $\text{DMSO}-d_6$): 1.4 (3H, d, $J=6.4$ Hz), 1.5 (1H, m), 1.91 (1H, m), 2.77 (2H, m), 3.52 (1H, m), 5.87 (2H, s), 7.12 (1H, t, $J=7.2$ Hz), 7.34 (1H, d, $J=6.4$ Hz), 7.45 (5H, m), 7.97 (1H, d, $J=7.6$ Hz).

^{13}C NMR (100.7 MHz, $\text{DMSO}-d_6$): 17.1, 21.2, 29.9, 57.5, 97.3, 113.7, 117.8, 123.4, 126.8, 127.7, 128.5, 128.7, 128.7, 128.9, 134.6, 137.4, 142.7, 156.8, 175.4. IR (KBr) ν : 3425, 3300, 1645, 1603, 1525 cm^{-1} ; MS: m/z 291 (M^+); *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.55; H, 6.21; N, 9.59.

3-Amino-5-methyl-2-(3-trifluoromethylphenyl)-6,7-dihydro-1H, 5H-pyrido[3,2,1-ij]-quinolin-1-on (4b). This compound was obtained as white powder.

Yield: 72%; mp 180–181°C; ^1H NMR (400.4 MHz, $\text{DMSO}-d_6$): 1.4 (3H, d, $J=6.4$ Hz), 1.5 (1H, m), 1.92 (1H, m), 2.77 (2H, m), 3.51 (1H, m), 6.0 (2H, s), 7.11 (1H, t, $J=7.6$ Hz), 7.34 (1H, d, $J=6.8$ Hz), 7.6 (3H, m), 7.96 (1H, d, $J=7.2$ Hz).

^{13}C NMR (100.7 MHz, $\text{DMSO}-d_6$): 17, 24.1, 29.8, 57.7, 97.1, 113.4, 117.6, 122.6, 123.6, 124.5, 124.8, 126.9, 128.5, 130.6, 132.5, 132.9, 137.3, 142.5, 156.8, 175.4. IR (KBr) ν : 3430, 3305, 1646, 1605, 1528 cm^{-1} ; MS: m/z 359 (M^+); *Anal.* Calcd for $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}$: C, 67.03; H, 4.78; N, 7.82. Found: C, 66.98; H, 4.72; N, 7.78.

REFERENCES AND NOTES

- [1] Hardtmann, G. E. US 4192876; C07D215/22 – (1980).
- [2] Erb, B.; Rigo, B.; Pirotte, B.; Couturier, D. *J Heterocycl Chem* 2002, 39, 15–28.
- [3] Heathcock, C. H.; Kleinman, E. F.; Binkley, E. C. *JACS* 1982, 104, 1054.
- [4] Kutrov, G. P.; Kovalenko, N. V.; Volovenko, Y. M. *Russ J Org Chem* 2008, 44, 257.
- [5] Kojima, E.; Fujimori, S.; Awano, K. US 4956372, C07D215/48 (1990).
- [6] Coppola G. M. *J Heterocycl Chem* 1978, 15, 645.
- [7] Li X.-G.; Cheng X.; Zhou Q.-L. *Synth Commun* 2002, 32, 2477.
- [8] Graheva, I. N.; Tochilkin, A. I. *Chem Heterocycl Comp* 1988, 65.
- [9] Campbell, K. N.; Kerwin, J. F.; La Forge, R. A.; Campbell, B. K. *JACS* 1946, 68, 1844.
- [10] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; Elsevier: Oxford, 2003; 609.