Transformations of 2-Aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines, Cycloadducts of the BiCl₃-Catalyzed Three-Component Povarov Reaction: Oxidation and Reduction Processes Towards New Potentially Bioactive 2-Arylquinoline Derivatives
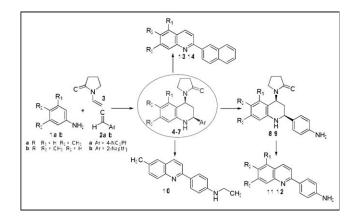
Vladimir V. Kouznetsov,* Carlos M. Meléndez Gómez, and John H. Bermúdez Jaimes

Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia
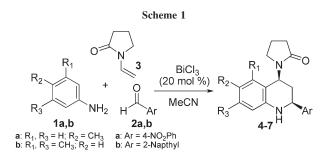*E-mail: kouznet@uis.edu.co

Synthesis and spectral characterization of new series of 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines and their aromatic analogs, 2-arylquinolines are reported. It was found that substituted tetrahydroquinoline precursors are easily prepared using BiCl₃-catalyzed three-component Povarov reaction between 4-nitrobenzaldehyde or 2-naphtylcarboxyaldehyde, anilines and *N*-vinylpyrrolidin-2-one, and could be transformed *via* oxidation and reduction processes into potentially bioactive 2-arylquinoline derivatives, unsubstituted at the C-4 position. The all set of (tetrahydro)quinolines were characterized by IR, ^{1}H and ^{13}C-NMR spectroscopy.

INTRODUCTION

Quinoline and tetrahydroquinoline structures are essential feature of many natural products. These heterocycles play a key role in heterocyclic and medicinal chemistry. Their syntheses by various methodologies have been published extensively [1–4]. Polyfunctionalized tetrahydroquinolines (THQs) are molecules of great interest in organic synthesis because many natural products present this system in their structure, and these compounds exhibit diverse biological activities [5–9]. Apart from their marked bioactivities, THQs are also important and reliable precursors in quinoline preparation, another group of heterocyclic molecules that has a great number of pharmacological properties [10]. However, general syntheses of functionalized quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions are less common [11], and often suffer from harsh reaction conditions, expensive reagents,

or both. Moreover, the number of these commercially available reagents is exceedingly small that limits the preparation of quinolines substituted on the quinoline aryl moiety.

For these reasons, the synthesis of new THQs is still of great interest. An efficient route for the preparation of THQs is the acid-catalyzed Povarov reaction that is classified as imino Diels-Alder cycloaddition [11,12]. Moreover, this methodology that permits the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to afford new tetrahydroquinolines, can overcome synthetic limitations for the construction of functionalized quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions and are useful tool for the generation of quinoline derivatives with several degrees of structural diversity. Then, appropriate choice of aldehydes and alkenes in this cycloaddition reaction

Scheme 1

provides a facile entry to heterocyclic systems which is an essential moiety in many active pharmaceuticals.

As a part of our research program on the *N*-aryl imines towards the synthesis of bioactive substituted tetrahydroquinolines and quinolines, we are pursuing investigations on the synthesis of small drug-like (tetrahydro)quinoline molecules containing C-2 aryl fragment, those synthesis could be accomplished *via* cycloaddition reactions. We now want to report simple preparation of new 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines using BiCl₃-catalyzed three component Povarov reaction between 4-nitrobenzaldehyde or 2-naphtylcarboxyaldehyde, anilines and *N*-vinylpyrrolidin-2-one (NVP), and their transformations into potentially bioactive 2-arylquinoline derivatives, unsubstituted at the C-4 position.

RESULTS AND DISCUSSION

Planning synthesis of new 2-arylquinoline derivatives, we paid attention the following considerations: (i) *N*-vinylpyrrolidin-2-one (NVP) is very active electron-rich alkene in this reaction [13–16] and it is an available, stable, and cheap reagent. Moreover, 2-oxopyrrolidinyl moiety on the tetrahydroquinoline ring could be easily removed; (ii) 4-nitrobenzaldehyde could provide 4-aminophenyl fragment, those synthetic utilization to construct *N*-heterocycles is well recognized; (iii) 2-naphtylcarboxyaldehyde was chosen for the preparation of new 2-naphtylquinolines, aromatic planar molecules, and interesting models in biological tests (anticancer activity).

So, using BiCl₃-catalyzed (20 mol %) three component Povarov reaction between anilines **1a,b**, aldehydes **2a,b** and NVP **3** in MeCN, a new series of the functionalised THQs **4–7** was easily prepared in excellent yields (Scheme 1).

Structural elucidation of obtained solid substances (Table 1) was started with IR analysis that indicated at the presence of characteristic intensive bands in zone 3394, 3271, and 1666 cm^{-1} (NH and C=O for all comp. **4–7**), and also 1512 and 1342 cm^{-1} (NO₂ for comp. **4,5**). From their spectral analyses (¹H-, ¹³C-NMR

and COSY), it was found that the *cis*-diastereoisomer was prevalent in all of the cases studied. For example, from ¹H-NMR spectrum of comp. **4**, it could clearly observed two doublets of doublets at 5.69 ppm ($J_{3,4}$ = 11.1 and 6.4 Hz) and 4.65 ppm ($J_{2,3}$ = 10.7 and 3.1 Hz) that correspond to the THQ protons 4-H and 2-H, respectively.

The large vicinal coupling confirmed strongly axial–axial dispositions of the THQ protons 4-H and 2-H and, consequently, the substituents at C-4 and C-2 should have an equatorial disposition that indicates at a *cis* configuration of the THQ ring.

Having stable solid THQ derivatives in our hands, we realized some simple chemical transformations, which resulted in the efficient preparation of quinoline molecules **10–14** (Scheme 2). First, to obtain new 2-(4-aminophenyl)-THQs **8,9**, we analysed reduction process of nitro derivatives **4,5** under different reaction conditions. The conventional hydrogenation process [H₂/Pd-C (10%)/MeOH] always gave in moderate yields the desired products, contaminated with side-products. The change of solvent nature (MeOH → MeOH/CH₂Cl₂) in H₂/Pd-C hydrogenation reaction (method **A**) did not improve this situation. Thus, we addressed to another reduction reaction that uses NaBH₄ and NiCl₂ in MeOH/CH₂Cl₂ (method **B**) that resulted an efficient and selective system, which satisfied to our plans. Under these reaction conditions, it was possible to prepare desired *cis*-2-(4-aminophenyl)-THQs **8,9** in good yields. However, it should be noted that among different attempts to find ideal conditions for hydrogenation process of comp. **4** we tested also a H₂/Pd-C/MeCN-MeOH system (method **C**) that allowed obtaining an unexpected quinoline product **10**. This formation could be assumed as a result of subsequent three processes: (1)

Table 1

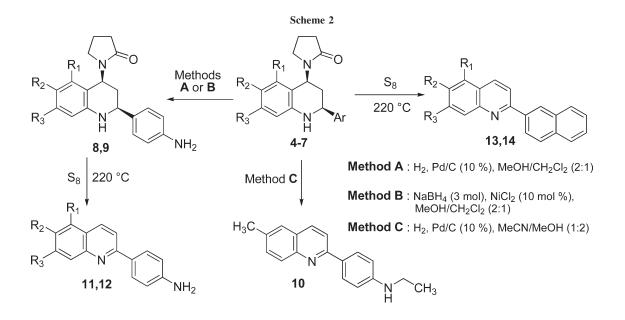Tetrahydroquinolines **4–9** and quinolines **10–14** prepared by imino Diels-Alder reaction.

Comp.	R_1	R_2	R_3	Ar	Mp (°C)	Yield (%)
4	H	Me	H	4-NO₂Ph	222–223	95
5	Me	H	Me	4-NO₂Ph	239–240	98
6	H	Me	H	2-Naphtyl	214–215	72
7	Me	H	Me	2-Naphtyl	182–183	90
8	H	Me	H	4-NH₂Ph	233–234	95[a] (54)[b]
9	Me	H	Me	4-NH₂Ph	183–185	97[a]
10	H	Me	H	4-NHEtPh	149–151	47[c]
11	H	Me	H	4-NH₂Ph	178–179	89[a]
12	Me	H	Me	4-NH₂Ph	115–116	73[a]
13	H	Me	H	2-Naphtyl	160–161	87
14	Me	H	Me	2-Naphtyl	86–87	73

[a] Obtained by method **B**.
[b] Obtained by method **A**.
[c] Obtained by method **C**.

Scheme 2

ring aromatization reaction with pyrrolidine fragment elimination, (2) nitro group reduction into amine function, (3) N-ethylation of amine group to give *N*-ethylamino derivative **10** (Scheme 2). Its quinoline structure was strongly confirmed by ^{1}H-, ^{13}C-NMR spectra and 2D NMR spectroscopy.

Other quinoline derivatives **11–14** were easily prepared from the respective tetrahydroquinolines by use of their rapid fusion with elemental sulfur following our developed protocol [17]. These quinoline molecules are stable, yellowish substances that were purified by means of a short chromatographic column (Table 1).

Finally, the obtained THQs **6–9** were subjected into oxidation process using our rapid fusion-sulfur protocol to prepare new corresponding2-(4-aminophenyl)quinolines **11,12** and 2-(2-naphtyl)quinolines **13,14**. This aromatization reaction was achieved by its fusion with elemental sulfur at 220–240°C in 5–10 min. All new compounds were directly isolated without previous extraction using flash column chromatographic and were completely identified using NMR spectroscopy.

In conclusion, we reported the efficient synthesis of new series of 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines and their aromatic analogs, 2-arylquinolines, unsubstituted at the C-4 position. These potentially bioactive 2-(aryl)quinoline derivatives could be important models in antioxidant, antiparasitic or/and anticancer studies [18].

EXPERIMENTAL

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Lumex Infralum FT-02 spectrophotometer in KBr. ^{1}H, ^{13}C-NMR spectra were recorded on Bruker AM-400 spectrometer. Chemical shifts are reported in ppm (δ) relative to the solvent peak (CHCl$_3$ in CDCl$_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; td, triplet of doublets; q, quartet; sp, septet; m, multiplet; b, broad. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS Chemstation Data system was used for ms identification at 70 EV using a 60 m capillary column coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin–Elmer 2400 Series II analyzer and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminium sheet.

General procedure for the imino Diels-Alder reaction of anilines, aldehydes and NVP. To a solution of the appropriate aniline (1.00 mmol) and aldehyde (1 mmol) in anhydrous CH$_3$CN (20 mL) under N$_2$ atmosphere, was added 20 mol % BiCl$_3$ (0.57 mmol) and *N*-vinylpyrrolidone (1.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with a solution of Na$_2$CO$_3$. The organic layer was separated, and dried with Na$_2$SO$_4$. The organic solvent was removed *in vacuo* and the product purified with chromatography column (hexane/ethyl acetate).

1-[6-Methyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (4). The compound **4** was obtained in 95% yield, yellow solid, m.p. 222–223°C. IR (potassium bromide): ν 3394, 2947, 2916, 1666, 1620 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 8.20 (2H, d, $J = 8.7$ Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 7.61 (2H, d, $J = 8.7$ Hz, 2-H$_{Ar}$ and 6-H$_{Ar}$), 6.90 (1H, dd, $J = 8.0$, 1.7 Hz, 7-H$_{THQ}$), 6.68 (1H, s, 5-H$_{THQ}$), 6.57 (1H, d, $J = 8.1$ Hz, 8-H$_{THQ}$), 5.69 (1H, dd, $J = 11.1$, 6.4 Hz, 4-H$_{aTHQ}$), 4.65 (1H, dd, $J = 10.7$, 3.1 Hz, 2-H$_{aTHQ}$), 4.03 (1H, br.s, N—H), 3.21 (2H, t, $J = 6.9$ Hz, 5-H$_{Pyrr}$), 2.59–2.41 (2H, m, 3-H$_{Pyrr}$), 2.23 (3H, s, 6-Me$_{THQ}$), 2.13–1.99 (4H, m, 4-H$_{Pyrr}$ and 3-H$_{THQ}$). ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 175.8, 150.6, 147.4, 142.9, 129.0, 128.1, 127.3 (2C), 126.9, 123.9 (2C), 118.8, 115.4, 56.0, 48.1, 42.2, 35.3, 31.3, 20.5, 18.1. gc-ms t_R: 44.57 min,

m/z: 351 (molecular ion). *Anal. Calcd.* for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.40; H, 5.99; N, 11.97.

1-[5,7-Dimethyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (5). The compound **5** was obtained in 98% yield, yellow solid, m.p. 239–240°C. IR (potassium bromide): ν 3271, 2972, 2916, 2854, 1666 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 8.21 (2H, d, J = 8.7 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 7.62 (2H, d, J = 8.6 Hz, 2-H$_{Ar}$ and 6-H$_{Ar}$), 6.47 (1H, s, 6-H), 6.37 (1H, s, 8-H$_{THQ}$), 5.57 (1H, t, J = 8.5 Hz, 4-H$_{aTHQ}$), 4.48 (2H, dd, J = 10.6, 2.5 Hz, 2-H$_{aTHQ}$), 3.97 (1H, br.s, N—H), 3.08 (1H, ddd, J = 9.7, 8.7, 5.4 Hz, 5-H$_{ePyrr}$), 2.82 (1H, ddd, J = 9.9, 8.4, 6.0 Hz, 5-H$_{aTHQ}$), 2.43-2.27 (3H, m, 3-H$_{Pyrr}$ and 3-H$_{eTHQ}$), 2.23 (3H, s, 5-Me$_{THQ}$), 2.10 (1H, t, J = 12.0 Hz, 3-H$_{aTHQ}$), 2.06 (3H, s, 7-Me$_{THQ}$), 1.94-1.72 (2H, m, 4-H$_{Pyrr}$). ¹³C-NMR (CDCl₃, 100 MHz): δ 174.5, 150.5, 147.3, 146.7, 138.3, 138.2, 127.2 (2C), 123.9 (2C), 122.8, 114.9, 114.3, 55.4, 46.5, 42.4, 36.3, 31.0, 21.0, 19.3, 17.8. gc-ms t_R: 49.65 min, m/z: 365 (molecular ion). *Anal. Calcd.* for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.01; H, 6.35; N, 11.48.

1-(6-Methyl-2-(2-naphtyl)-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (6). The compound **6** was obtained in 72% yield, white solid, m.p. 214–215°C. IR (potassium bromide): ν 3332, 3055, 3024, 2954, 2916 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 7.88 (1H, s, 1-H$_{Napht}$), 7.85-7.82 (3H, m, 4-H$_{Napht}$, 5-H$_{Napht}$ and 8-H$_{Napht}$), 7.52-7.50 (1H, m, 3-H$_{Napht}$), 7.49-7.45 (2H, m, 6-H$_{Napht}$ and 7-H$_{Napht}$), 6.89 (1H, d, J = 7.9 Hz, 8-H$_{THQ}$), 6.70 (1H, s, 5-H$_{THQ}$), 6.55 (1H, d, J = 8.0 Hz, 7-H$_{THQ}$), 5,74 (1H, t, J = 8.9, 4-H$_{aTHQ}$), 4.71 (1H, t, J = 6.9 Hz, 2-H$_{aTHQ}$), 3.99 (1H, br.s, N—H), 3.28-3.18 (2H, m, 5-H$_{Pyrr}$), 2.50-2.42 (2H, m, 3-H$_{Pyrr}$), 2.24 (3H, s, 6-Me$_{THQ}$), 2.18-2.14 (2H, m, 3-H$_{THQ}$), 2.04-1.97 (2H, m, 4-H$_{Pyrr}$). ¹³C-NMR (CDCl₃, 100 MHz): δ 175.8, 143.6, 140.6, 133.4, 133.1, 128.9, 128.5, 127.8, 127.7, 127.5, 127.1, 126.2, 125.9, 125.0, 124.6, 119.0, 115.2, 56.6, 48.5, 42.3, 35.4, 31.4, 20.6, 18.2. gc-ms t_R: 55.83 min, m/z: 356 (molecular ion). *Anal. Calcd.* for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.84; H, 6.78; N, 7.84.

1-[5,7-Dimethyl-2-(2-naphtyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (7). The compound **7** was obtained in 90% yield, white solid, m.p. 182–183°C. IR (potassium bromide): ν 3332, 3047, 3016, 2978, 2924 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 7.87 (1H, s, 1-H$_{Napht}$), 7.84-7.81 (3H, m, 4-H$_{Napht}$, 5-H$_{Napht}$ and 8-H$_{Napht}$), 7.51-7.50 (1H, m, 3-H$_{Napht}$), 7.48-7.45 (2H, m, 6-H$_{Napht}$ and 7-H$_{Napht}$), 6.44 (1H, s, 6-H$_{THQ}$), 6.36 (1H, s, 8-H$_{THQ}$), 5.62 (1H, t, J = 8.5 Hz, 4-H$_{aTHQ}$), 4.50 (1H, d, J = 10.6 Hz, 2-H$_{aTHQ}$), 4.01 (1H, br.s, N—H), 3.16-3.10 (1H, m, 5-H$_{ePyrr}$), 2.85-2.70 (1H, m, 5-H$_{aPyrr}$), 2.46-2.26 (3H, m, 3-H$_{Pyrr}$ and, 3-H$_{eTHQ}$), 2.23 (3H, s, 7-Me$_{THQ}$), 2.19-2.14 (1H, m, 3-H$_{aTHQ}$), 2.08 (3H, s, 5-Me$_{THQ}$), 1.92-1.97 (2H, m, 4-H$_{Pyrr}$). ¹³C-NMR (CDCl₃, 100 MHz): δ 174.4, 147.5, 140.4, 138.3, 138.0, 133.4, 133.0, 128.4, 127.8, 127.6, 126.2, 125.9, 124.8, 124.6, 122.3, 115.1, 114.1, 55.9, 46.8, 42.4, 36.4, 31.1, 21.0, 19.4, 17.8. gc-ms t_R: 54.14 min, m/z: 370 (molecular ion). *Anal. Calcd.* for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 81.06; H, 7.03; N, 7.54.

General procedure for the hydrogenation with H₂/Pd/C (method A). To a solution of nitro derivative (**4**) (2.85 mmol) in MeOH:CH₂Cl₂ (2:1) was added Pd/C (10% p/p). Molecular hydrogen was injected to the system; the reaction mixture was stirred at room temperature for 24 h. The organic layer was filtered in a chromatographic column (silica gel), the solvent was

removed *in vacuo* and the product was purified with chromatography column (hexane/ethyl acetate).

1-[6-Methyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (8). The compound (**8**) was obtained in 54% yield, yellow solid, m.p. 233–234°C. IR (potassium bromide): ν 3440, 3379, 3356, 3240, 2947, 2916, 1666 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 8.28 (1H, d, J = 8.4 Hz, 2-H$_{Ar}$), 8.18 (1H, d, J = 8.3 Hz, 6-H$_{Ar}$), 7.70 (2H, dd, J = 11.5, 8.7 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 6.90 (1H, bt, J = 5.5 Hz, 7-H$_{THQ}$), 6.69 (1H, s, 5-H$_{THQ}$), 6.55 (1H, t, J = 6.9 Hz, 8-H$_{THQ}$), 5.71 (1H, dd, J = 10.2, 6.9 Hz, 4-H$_{aTHQ}$), 4.62 (1H, ddd, J = 12.0, 10.6, 3.4 Hz, 2-H$_{aTHQ}$), 3.96 (1H, s, NH₂), 3.20 (2H, d, J = 5.9 Hz, 5-H$_{Pyrr}$), 2.59-2.43 (2H, m, 3-H$_{Pyrr}$), 2.23 (3H, s, 6-Me$_{THQ}$), 2.12-1.01 (4H, m, 3-H$_{THQ}$ and 4-H$_{Pyrr}$) ppm. gc-ms t_R: 25.34 min, m/z: 321 (molecular ion). *Anal. Calcd.* for $C_{20}H_{23}N_3O$ C, 74.74; H, 7.21; N, 13.07. Found: C, 74.75; H, 7.20; N, 13.05.

General procedure for reduction reaction with NiCl₂/ NaBH₄ (method B). To a mixture of nitro derivatives (**4,5**) (2.85 mmol) and nickel chloride (II) (0.28 mmol) in MeOH:CH₂Cl₂ (2:1), NaBH₄ (8.55 mmol) was added in small portions, keeping reaction system at 0°C. The reaction was stirred by 1 hour at room temperature and the organic layer was filtered and washed (methanol and distilled water), extracted with CH₂Cl₂ (3 × 10 mL) and dried under Na₂SO₄.

1-[6-Methyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (8). The compound (**8**) was obtained in 95% yield. Their physicochemical parameters were identical to product (**8**) obtained by method **A**.

1-[5,7-Dimethyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (9). The compound (**9**) was obtained in 97% yield, yellow solid, m.p. 255–258°C. IR (potassium bromide): ν 3440, 2916, 1666, 1620, 1589 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 8.29 (1H, d, J = 8.2 Hz, 2-H$_{Ar}$), 8.18 (1H, d, J = 8.1 Hz, 6-H$_{Ar}$), 7.55 (2H, d, J = 8.9 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 6.45 (1H, s, 6-H$_{THQ}$), 6.36 (1H, m, 8-H$_{THQ}$), 5.58 (1H, t, J = 8.5 Hz, 4-H$_{aTHQ}$), 4.42 (1H, t, J = 12.1 Hz, 2-H$_{aTHQ}$), 3.97 (2H, br.s, NH₂), 3.11 (1H, dd, J = 14.1, 8.5 Hz, 5-H$_{ePyrr}$), 2.82 (1H, dd, J = 15.3, 7.8 Hz, 5-H$_{aPyrr}$), 2.41-2.31 (3H, m, 3-H$_{Pyrr}$ and 3-H$_{eTHQ}$), 2.22 (3H, s, 5-Me$_{THQ}$), 2.11 (1H, t, J = 12.0 Hz, 3-H$_{aTHQ}$), 2.07 (3H, s, 7-Me$_{THQ}$), 1.85 (2H, dd, J = 13.8, 6.0 Hz, 4-H$_{Pyrr}$) ppm. gc-ms t_R: 26.62 min, m/z: 335 (molecular ion). *Anal. Calcd.* for $C_{21}H_{25}N_3O$ C, 75.19; H, 7.51; N, 12.53. Found: C, 75.18; H, 7.50; N, 12.55.

General procedure for the hydrogenation with H₂/Pd/C (method C). To a solution of nitro derivative (**4**) (2.85 mmol) in MeOH/MeCN (2:1) was added Pd/C (10% p/p). Molecular hydrogen was injected to the system; the reaction mixture was stirred at room temperature for 24 h. The organic layer was filtered in a chromatographic column (silica gel), the solvent was removed *in vacuo* and the product was purified with chromatography column (hexane/ethyl acetate).

2-(4-N-Ethylaminophenyl)-6-methylquinoline (10) The compound (**10**) was obtained in 46% yield, yellow solid, m.p. 149–151°C. IR (potassium bromide): ν 3394, 2961, 2916, 2854, 1605 cm⁻¹. ¹H-NMR (CDCl₃, 400 MHz): δ 8.02 (2H, d, J = 8.6 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 8.00 (1H, d, J = 8.1 Hz, 8-H$_{Qu}$), 7,99 (1H, d, J = 8.6 Hz, 3-H$_{Qu}$), 7.74 (1H, d, J = 8.7 Hz, 4-H$_{Qu}$), 7.50 (1H, s, 5-H$_{Qu}$), 7.49 (1H, d, J = 8.5 Hz, 7-H$_{Qu}$), 6.69 (2H, d, J = 8.7 Hz, 2-H$_{Ar}$ and 6-H$_{Ar}$), 3.79 (1H, br.s, N—H), 3.21 (2H, q, J = 7.1 Hz, —CH₂Me$_{Ar}$), 2.50 (3H, s, 6-Me$_{Qu}$), 1.26 (3H, t, J = 7.1 Hz, —CH₂$Me$$_{Ar}$) ppm. ¹³C-

NMR (CDCl$_3$, 100 MHz): δ 156.5, 149.4, 146.8, 135.6, 135.0, 131.5, 129.0, 128.5 (2C), 128.4, 126.6, 126.3, 118.2, 112.6 (2C), 38.2, 21.5, 14.7, ppm. gc-ms t_R: 26,50 min, m/z: 262 (molecular ion). *Anal. Calcd.* for C$_{18}$H$_{18}$N$_2$ C, 82.41; H, 6.92; N, 10.68. Found: C, 82.40; H, 6.93; N, 10.69.

General procedure for the aromatization with sulfur. The 2-(aminophenyl) and 2-(nitroaryl) substituted tetrahydroquinolines (**4-7**) were heated quickly (10–15 min) in the presence of elemental sulfur (S$_8$) to 220–230°C. The reaction mixture was adsorbed under silica gel and separated by chromatography column to afford the 2-arylquinolines.

2-(4-Aminophenyl)-6-methylquinoline (11). The compound (**11**) was obtained in 89% yield, yellow solid, m.p. 178–179°C. IR (potassium bromide): ν 3386, 3301, 3193, 3055, 3023 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 8.03 (1H, d, J = 8.7 Hz, 4-H$_{Qu}$), 8.01 (3H, dt, J = 8.6, 2.0 Hz, 2-H$_{Ar}$ and 6-H$_{Ar}$), 7.92 (1H, dd, J = 8.8, 1.3 Hz, 8-H$_{Qu}$)7.76 (1H, d, J = 8.6 Hz, 3-H$_{Qu}$), 7.53 (1H, s, 5-H$_{Qu}$), 7.52 (1H, dd, J = 8.8, 1.3 Hz, 7-H$_{Qu}$), 6.80 (2H, dt, J = 8.6, 2.0 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 3.85 (2H, br.s, NH$_2$), 2.53 (3H, s, 6-Me$_{Qu}$) ppm. ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 156.4, 147.6, 146.9, 135.8, 135.3, 131.6, 130.1, 129.1, 128.6 (2C), 126.8, 126.3, 118.3, 115.1 (2C), 21.5 ppm. gc-ms t_R: 25.13 min, m/z: 234 (molecular ion). *Anal. Calcd.* for C$_{16}$H$_{14}$N$_2$ C, 82.02; H, 6.02; N, 11.96. Found: C, 82.00; H, 6.03; N, 11.97.

2-(4-Aminophenyl)-5,7-dimethylquinoline (12). The compound (**12**) was obtained in 73% yield, yellow solid, m.p. 115–116°C. IR (potassium bromide): ν 3433, 3317, 3201, 3032, 2962 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 8.23 (1H, d, J = 8.9 Hz, 3-H$_{Qu}$), 8.01 (2H, d, J = 8.5 Hz, 2-H$_{Ar}$ and 6-H$_{Ar}$), 7.75 (1H, s, 8-H$_{Qu}$), 7.73 (1H, d, J = 8.9 Hz, 4-H$_{Qu}$), 7.13 (1H, s, 6-H$_{Qu}$), 6.79 (2H, d, J = 8.5 Hz, 3-H$_{Ar}$ and 5-H$_{Ar}$), 3.85 (2H, br.s, NH$_2$), 2.63 (3H, s, 7-Me$_{Qu}$), 2.50 (3H, s, 5-Me$_{Qu}$) ppm. ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 156.6, 148.8, 147.6, 139.2, 133.8, 132.6, 130.0, 128.6 (2C), 128.5, 126.7, 124.1, 117.0, 115.1 (2C), 21.8, 18.4 ppm. gc-ms t_R: 26.94 min, m/z: 248 (molecular ion). *Anal. Calcd.* for C$_{17}$H$_{16}$N$_2$ C, 82.22; H, 6.49; N, 11.28. Found: C, 82.23; H, 6.51; N, 11.30.

6-Methyl-2-(2-napthyl)quinoline (13). The compound (**13**) was obtained in 87% yield, white solid, m.p. 160–161°C. IR (KBr): ν 3055, 3008, 2916, 2854, 1589 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 8.58 (1H, s, 1-H$_{Napht}$), 8.35 (1H, d, J = 8.5 Hz, 4-H$_{Napht}$), 8.12-8.00 (2H, m, 3-H$_{Qu}$ and 8-H$_{Qu}$), 7.99-7.95 (3H, m, 4-H, 3-H$_{Napht}$, 8-H$_{Napht}$), 7.89-7.56 (1H, m, 5-H$_{Napht}$), 7.58 (1H, s, 5-H$_{Qu}$), 7.58-7.56 (1H, m, 7-H$_{Qu}$), 7.53-7.49 (2H, m, 6-H$_{Qu}$ and 7-H$_{Napht}$), 2.54 (3H, s, 6-Me$_{Qu}$) ppm. ^{13}C-NMR (CDCl$_3$, 100 MHz): δ156.2, 146.9, 137.0, 136.2, 136.1, 133.7, 133.5, 131.9, 129.4, 128.8, 128.5, 127.7, 127.2, 126.9, 126.5, 126.3, 126.2, 125.0, 119.1, 21.6 ppm. gc-ms t_R: 27.02 min, m/z: 269 (molecular ion). *Anal. Calcd.* for C$_{20}$H$_{15}$N C, 89.19; H, 5.61; N, 5.20. Found: C, 89.20; H, 5.62; N, 5.21.

5,7-Dimethyl-2-(2-napthyl)quinoline (14). The compound (**14**) was obtained in 73% yield, white solid, m.p. 86–87°C. IR (KBr): ν 3055, 2970, 2900, 2854, 1620 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 8.58 (1H, s, 1-H$_{Napht}$), 8.34 (1H, dd, J

= 8.7, 1.5 Hz, 4-H$_{Napht}$), 8.28 (1H, d, J = 8.7 Hz, 3-H$_{Qu}$), 7.97-7.94 (1H, m, 8-H$_{Napht}$), 7.95 (1H, d, J = 8.5 Hz, 3-H$_{Napht}$), 7.91 (1H, d, J = 8.7 Hz, 4-H$_{Qu}$), 7.88–7.85 (1H, m, 5-H$_{Napht}$), 7.85 (1H, s, 8-H$_{Qu}$), 7.50 (2H, dd, J = 6.2, 3.2 Hz, 6-H$_{Napht}$ and 7-H$_{Napht}$), 7.17 (1H, s, 6-H$_{Qu}$), 2.63 (3H, s, 7-Me$_{Qu}$), 2.52 (3H, s, 5-Me$_{Qu}$) ppm. ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 156.5, 148.9, 139.5, 137.0, 133.9, 133.8, 133.5, 132.9, 129.1, 128.8, 128.4, 127.7, 127.0, 126.9, 126.5, 126.2, 125.0, 124.6, 117.8, 21.8, 18.5 ppm. gc-ms t_R: 29.02 min, m/z: 283 (molecular ion). *Anal. Calcd.* for C$_{21}$H$_{17}$N C, 89.01; H, 6.05; N, 4.94. Found: C, 89.02; H, 6.04; N, 4.93.

REFERENCES AND NOTES

[1] Jones, G. In Pyridines and Their Benzo Derivatives; Katritzky, A., Eds.; Pergamon Press: Oxford, 1984, Vol. 2, pp 395–510.

[2] Katrizky, A. R.; Rachwal, S.; Rachwal, B. Tetrahedron 1996, 52, 15031.

[3] Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. J. Heterocycl Chem 1998, 35, 761.

[4] Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. Curr Org Chem 2005, 9, 141.

[5] Kouznetsov, V.; Vargas, L.; Leal, S.; Mora, U.; Coronado, C.; Meléndez, C.; Romero, A.; Escobar, P. Lett Drug Des Discov 2007, 4, 293.

[6] Meléndez, C.; Kouznetsov, V.; Sortino, M.; Álvarez, S.; Zacchino, S. Bioorg Med Chem 2008, 16, 7908.

[7] Vargas, L.; Castelli, M.; Kouznetsov, V.; Urbina, J.; López, S.; Sortino, M.; Enriz, R.; Ribas, J.; Zacchino, S. Bioorg Med Chem 2003, 11, 1531.

[8] Nandhakumar, R.; Suresh, T.; Calistus, A.; Rajesh, K.; Mohan, P. Eur J Med Chem 2007, 42, 1.

[9] Bekhit, A.; El-Sayed, O.; Aboulmagd, E.; Park, J. Eur J Med Chem 2004, 39, 249.

[10] Kariba, R.; Houghton, P.; Yenesew, A. J Nat Prod 2002, 65, 566.

[11] Katrizky, A. R.; Rachwal, B.; Rachwal, S. J Org Chem 1995, 60, 3993.

[12] Kouznetsov, V. V. Tetrahedron 2009, 65, 2721.

[13] Povarov, L.S. Russ Chem Rev 1967, 36, 656.

[14] Zhang, W.; Guo, Y.; Liu, Z.; Jin, X.; Yang, L.; Liu, Z.-L. Tetrahedron 2005, 61, 1325.

[15] Han, B.; Jia, X.-D.; Jin, X.-L.; Zhou, Y.-L.; Yang, L.; Liu, Z.-L.; Yu, W. Tetrahedron Lett 2006, 47, 3545.

[16] Srinivasa, A.; Mahadevan, K. M.; Hulikal, V. Monatsh Chem 2008, 139, 255.

[17] Kouznetsov, V.; Mora U. Lett Org Chem 2006, 3, 699.

[18] Antiparasitic and cytotoxic activities for this new series of compounds will be published in due course.