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SYNTHESIS AND NMR SPECTROSCOPIC CHARACTERISTICS OF NOVEL POLYSUBSTITUTED QUINOLINES INCORPORATING FUROXAN MOIETY

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Abstract – 5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline (**1**) and 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carbaldehyde (**2**) were synthesized. The condensation of **1** with some nitrobenzaldehydes catalyzed by acetic acid under mild conditions gave four styrylquinolines (**1a-d**). The condensation of **2** with methyl phenyl ketones catalyzed by potassium hydroxide at room temperature afforded six polysubstituted α,β-unsaturated ketones (**2a-f**). All proton and carbon signals of obtained compounds were assigned based on analyzing the spin–spin splitting patterns and on the cross peaks in their HSQC and HMBC spectra. ROESY spectrum analysis showed that for (*E*)-3-(quinolin-2-yl)-1-phenylprop-2-en-1-ones Hα resonated in a weaker field as compared to Hβ.

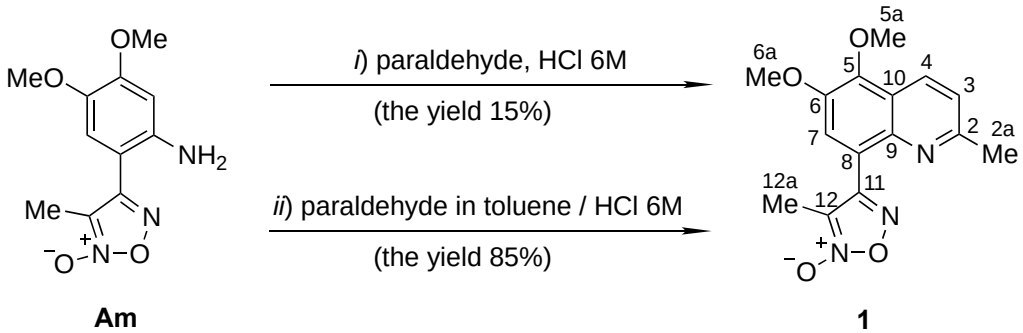
Quinolines have long attracted attention owing to their significant biological and pharmacological properties such as antimalarial,[1,2] antituberculosis,[3-5] antibacterial,[6,7] and anticancer.[8,9] Thus, quinoline ring is considered a core pharmacophore in the design of many drugs such as antimalarial chloroquine, mefloquine and primaquine,[10] antituberculosis bedaquiline,[11] and other diarylquinolines.[12] The increasing resistance against many antibiotic drugs has forced chemists to develop synthetic strategies toward novel biologically active molecules. A strategy that has attracted considerable attention in current medicinal chemistry is based on the conjugation of two biologically active molecules into one hybrid compound. In recent years several classes of quinoline based structural hybrids of various bioactive heterocycles as potential antimicrobial agents have yielded promising results in primary biological evaluation.[13-16] The

quinoline based molecule classes reported in these works are pyrazoles, thiazoles, 4-thiazolidinones, isoindolin-1-one, pyrimidines and 2-pyridones.

It is well known that furoxans possess remarkable biological activities, such as antimicrobial and antiparasitic properties, mutagenic, and anticancer effects, anti-aggregating and vasorelaxant activity.[17,18] Several classes of hybrid compounds, obtained combining appropriate pharmacophoric groups with NO-releasing furoxan moiety (NO-donor), have been described.[19-21]

Some time ago, we focused our attention to several natural arylolefins (eugenol, methyleugenol, safrole, anethole) from vegetable essential oils that could act as good substrates in order to prepare heterocyclic compounds. For example, 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**Am**), which was synthesized from methyleugenol, acted as a key compound for preparation of some series of imines, azo compounds, 1,3-thiazolidin-4-ones and quinazolines.[22-24] In addition, several obtained compounds exhibit good antimicrobial activity toward Gram positive *Staphylococcus aureus* (MIC = 12.5 μg/mL)[21] and high in vitro cytotoxicity on three cell lines, hepatocellular carcinoma (Hep-G2), human lung carcinoma (LU-1), and human breast carcinoma (MCF-7) with IC_{50} = 2.1-2.2 μM.[24] This report presents the results of synthesis and NMR characteristics of a series of polysubstituted quinolines incorporating furoxan moiety derived from 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**Am**).

The key compound, 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline (**1**), for preparation of the title compounds is synthesized according to Doebner-Miller method form 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**Am**).[22] The traditional one-phase solvent system method gave **1** with an yield of no more than 15%. Using two-phase solvent system method we obtained **1** with the yield of 85%, as described in Scheme 1 (The numeration on presented structures is specifically used for NMR analysis).



Scheme 1

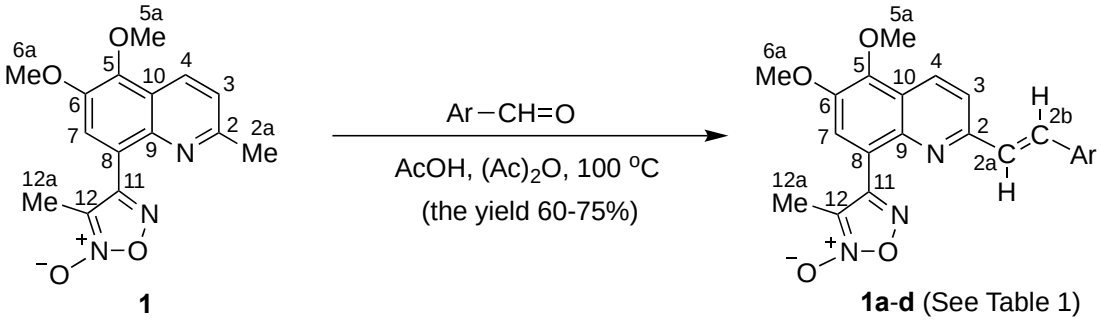
In both two manners *i* and *ii*, paraldehyde (2,4,6-trimethyl-1,3,5-trioxane) is gradually decomposed into acetaldehyde which undergoes a crotonic condensation to afford crotonaldehyde for cyclocondensation with **Am** to form **1**. For manner *i*, crotonaldehyde, on heating in strong acidic medium, also is further

polymerized. This polymerization not only decreased the cyclocondensation but also created a black resin that makes the isolation of the target product dificult. For manner *ii*, most crotonaldehyde dissolve into toluene phase where only traces of acid are present, thereby reducing the polymerization. Furthermore the toluene phase also dissolves the black resin, leaving compound **1** as quinolinium salt in the aqueous acid phase, thus facilitating the separation of compound **1** (see experimental section).

The structure of **1** was examined by IR, MS, ^{1}H, ^{13}C, and HMBC spectra. The IR spectrum of **1** differs from that of **Am** in the absence of NH_2 signal. The ESI HRMS positive mode (+MS) of **1** showed pseudomolecular ion $(M+H)^+$ with relative intensity of 100% at *m/z* = 302.1132, this is corresponding to formula $C_{15}H_{16}N_3O_4$ (M = 302.1141 au) and consistent with molecular formula of **1** ($C_{15}H_{15}N_3O_4$, M = 301.1063). In ^{1}H NMR spectrum of **1** there are three aromatic proton signals, two methoxy group signals and two methyl group signals relative to two aromatic proton, two methoxy group signals and one methyl group signal in **Am**, respectively. In ^{13}C NMR spectrum of **1** there are four ^{13}C signals more than those of **Am**. These spectral features demonstrated that the quinoline ring closure has been achieved.

Upon the treating of **1** with one equivalent of SeO_2 in dioxane at 80 ^{o}C, it is oxidized to form 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carbaldehyde (**2**) of the yield 78%, but with two equivalents of SeO_2 in dioxane at 100 ^{o}C, instead of **2**, 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)-quinoline-2-carboxylic acid (**3**) was obtained with the yield 72%. The strong absorption bands of C=O group in IR spectra of **2** and **3** appear at 1718 and 1698 cm^{-1}, respectively. Unlike **1**, in the weak field region of the ^{1}H NMR spectrum of **2** a new singlet at δ = 10.01 ppm with intensity of 1H appears, while on the strong field side, there is no longer a methyl proton signal at δ = 2.61 ppm with intensity of 3H, showing that the methyl group was oxidized to carboxaldehyde group. Unlike **2**, in the weak field region of the ^{1}H NMR spectrum of **3** there is no longer the carboxaldehyde proton signal at δ = 10.01 ppm. The proton of $-CO_2H$ group of **3** does not give a signal since it is in a exchange with proton of moist water in the solvent *d*$_6$-DMSO. All proton and carbon signals of **1**, **2** and **3** assigned with the help of HMBC spectra are given in the experimental.

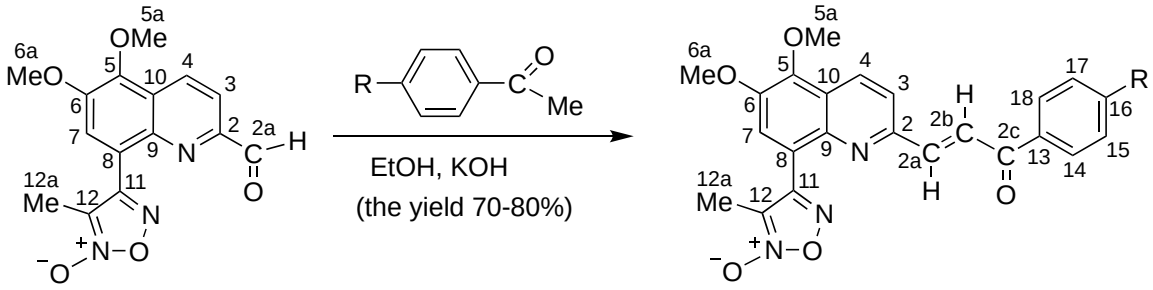
Compound **1** is subjected to condensation with some benzaldehydes to obtaine polysubstituted styrylquinolines since styrylquinolines have attracted continued interest of organic and medicinal scientists over the years because of their varied biological activities such as inhibitors of HIV-1,[25,26] antimalarial.[27] Uncatalyzed condensation of 2-methylquinolines and benzaldehydes is usually carried out at hight temperature, for example at 175-180 ^{o}C.[28] In order to avoid the isomerization of furoxan ring[29] at high temperature, we chose the acetic acid-catalyzed condensation in acetic anhydride heating at 100 ^{o}C. In this mild condition four styrylquinolines **1a-d** (Scheme 2 and Table 1) were obtained with the yields of 60-75%. They are yellow crystals melting at above 200 ^{o}C (Experimental).



1 **1a-d** (See Table 1)

Scheme 2

Compound **2** is subjected to the crotonic condensation with some methyl phenyl ketones to form a series of α,β-unsaturated ketones because some phenyl quinolyl α,β-unsaturated ketones are found to have effective and selective antitumor potential.[30,31] The condensation was carried out in ethanol with KOH as catalyst at room temperature. The obtained products **2a** – **f** (Scheme 3) are yellow needles crystals melting at above 200 °C (see Experimental).



2

R: H (**2a**); Me (**2b**); Cl (**2c**); Br (**2d**); OMe (**2e**); OEt (**2f**)

Scheme 3

The structures of **1a-d** and **2a-f** were determined by IR, MS, ^{1}H, ^{13}C, and 2D NMR spectra. All resonance signals in the NMR spectra of obtained compounds were accurately assigned based on analyzing the spin–spin splitting patterns, for some compounds, 2D NMR was also used. For example, two doublets at 7.73 and 8.20 ppm of **2a** (noted by 2’ and 2’’ in Figure 1 and 2) with J = 16 Hz are assigned to two *trans* ethylenic protons, but which doublet belongs to H2a, which doublet belongs to H2b remains to be clarified. In HSQC spectrum of **2a** (Figure 1) the cross peaks ***h*** and ***c*** show that H2’ (at 7,73 ppm) attaches to carbon signal at 142.6 ppm, H2’’ (at 8.20 ppm) attaches to carbon signal at 127.4 ppm, i.e. the order of chemical shifts of H2a and H2b is opposite to that of C2a and C2b. To solve this, it is necessary to first consider the conformations of **2a**. In order to have a stable conjugation system, for **2a** the quinoline ring, the benzene ring and the α,β-unsaturated ketone group must lie in the same plane (Scheme

4). Two confomations **I** and **III** are very unstable because H2a and H14 occupy each other's positions. Then, the ROESY spectra of **2a** (Figure 2) is anlyzed.

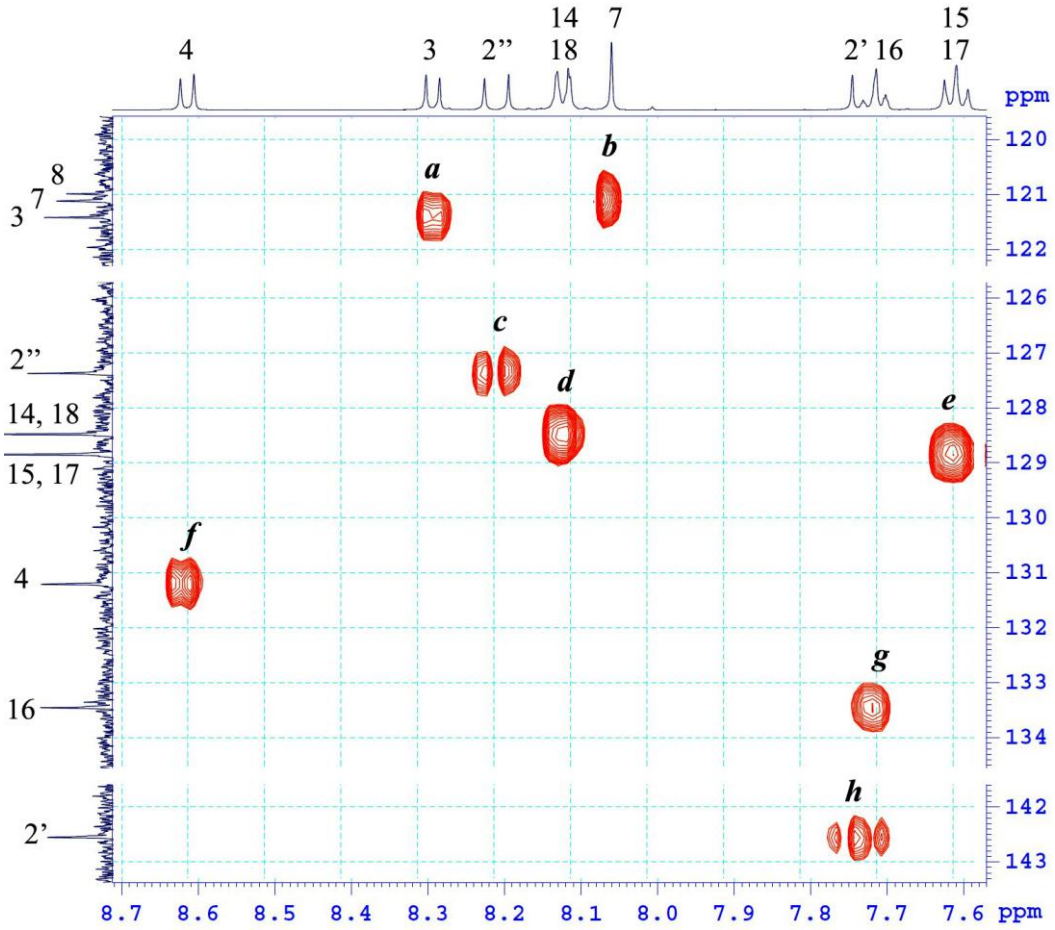
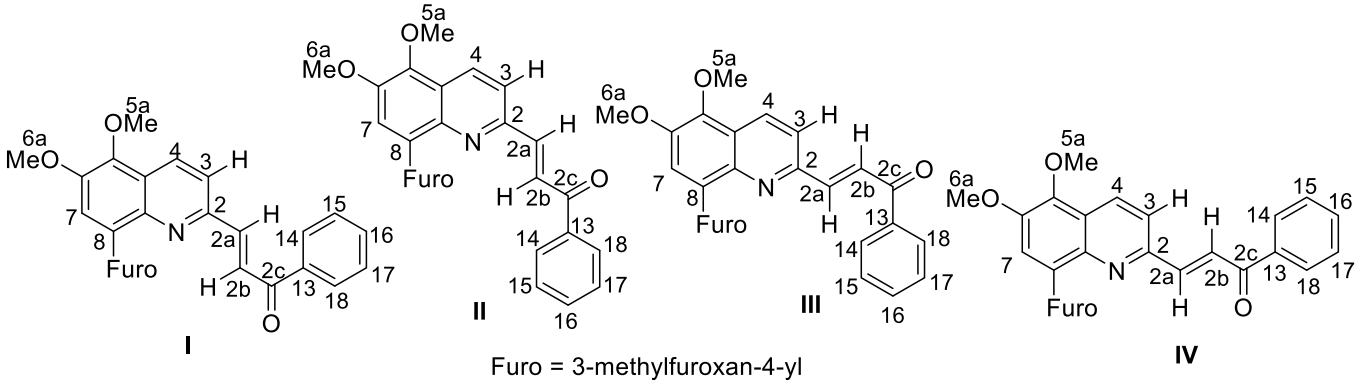


Figure 1. The partial HSQC spectrum of **2a**



Scheme 4

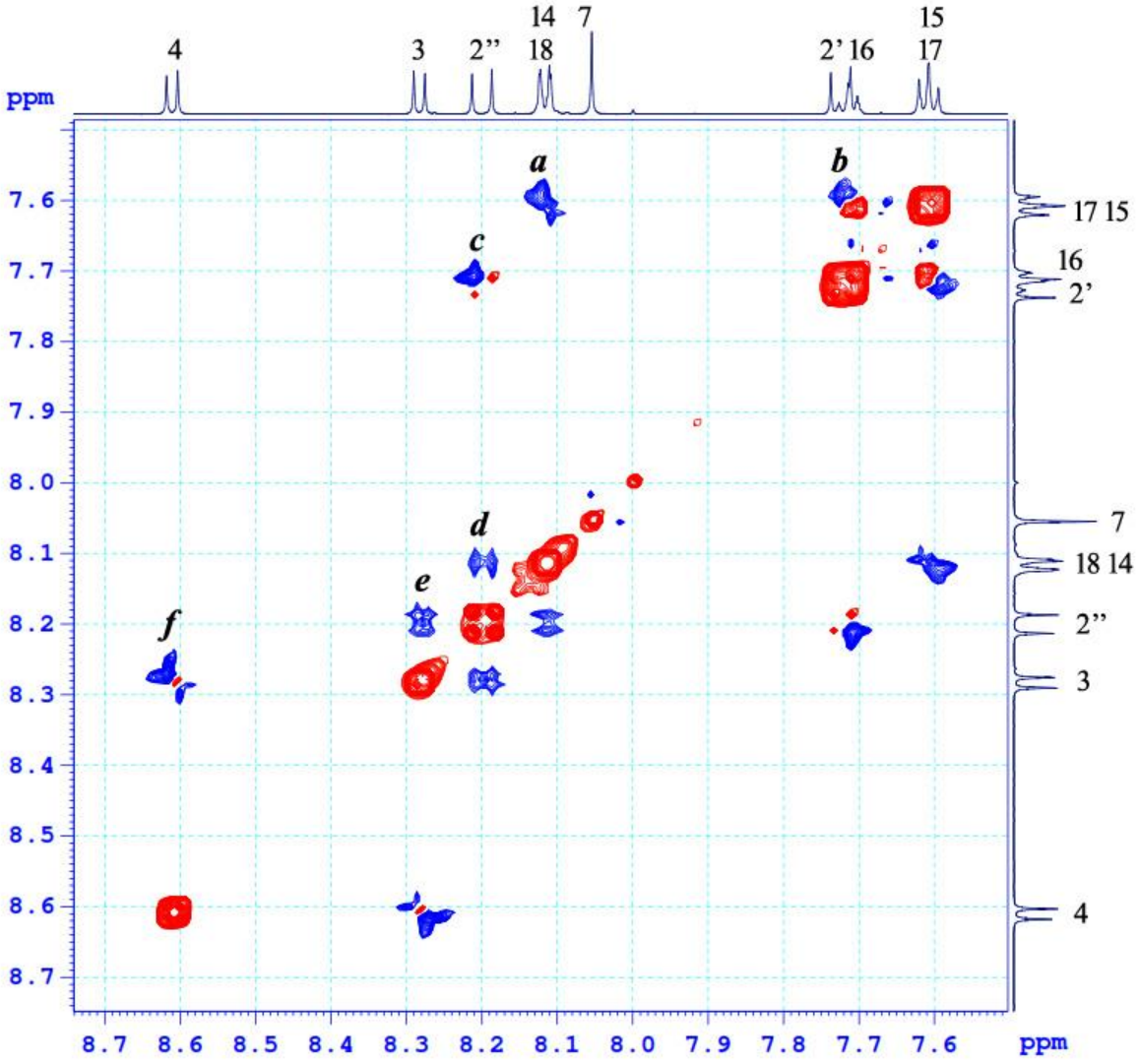


Figure 2. The partial ROESY spectrum of **2a**

In Figure 2 two doublets 2' and 2'' have cross peak ***c*** with one another. While the doublet 2'' has cross peaks ***d*** with H14/H18 and ***e*** with H3, the doublet 2' has no cross peak with H14/H18 nor cross peak with H3. This shows that, the proton 2'' is spatially near both H14/H18 and H3, and the proton 2' is spatially further away from them. It should be noted that ***b*** is the cross peak of H16 with H15/H17, and in full ROESY spectrum of **2a** there are no cross peaks of the furoxan methyl protons (H12a) with H2'and H2'' as well as with the quinoline protons and phenyl protons. These observations support the conformation **IV** and allow to infer that the signal 2" (at 8.20 ppm) belongs to H2b (Hα) and the signal 2' (at 7,73 ppm) belongs to H2a (Hβ), i.e. chemical shift of Hα (8.20 ppm) is much lager than that of Hβ (7,73 ppm). For α,β-unsaturated ketones, the chemical shift of Hβ is normally greater than that of Hα, surprisingly the opposite is true for **2a**. That anomaly can be explained by assuming that H2b (Hα) is deshielded by both benzene and quinoline rings as shown by structure **IV** in Scheme 4.

In conclusion, we have reported that 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine, an aromatic amine previously prepared from eugenol in *Ocimum sanctum* L. oil, is readily converted to 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline which then oxidized to 5,6-dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carbaldehyde. These new compounds were used as two key componds for the synthesis of 2-styrylquinolines and quinolin-2-yl chalcones incorporating furoxan moiety. Their biological activity is being studied further. All resonance signals in the NMR spectra of obtained compounds were accurately assigned based on analyzing the spin–spin splitting patterns, for some compounds, 2D NMR was also used. ROESY spectrum analysis showed that for (*E*)-3-(quinolin-2-yl)-1-phenylprop-2-en-1-ones Hα resonated in a weaker field as compared to Hβ.

EXPERIMENTAL

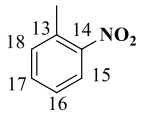
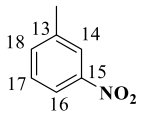
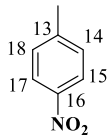
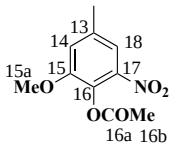
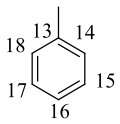
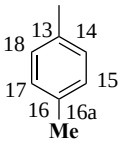
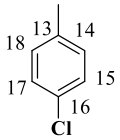
General

IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400–4000 cm^{-1}. ESI mass spectra were recorded using Agilent LC-MSD-Trap-SL series 1100 spectrometer. HRMS spectra were recorded using SCIEX X500R QTOF spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in d_6-DMSO with TMS as the internal standard, at 298–300 K.

Preparation

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline (1). To a solution of 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (2.51 g, 10 mmol, **Am**, previously prepared in reference[22]) in 6M HCl solution (60 mL) at 80 ºC a solution of toluene (30 mL) and paraldehyde (5 mL) was slowly added during 1 h under stirring. The reaction mixture was stirred for additional 4 h at 80 ºC. After cooling down to room temperature, the aqueous acid phase was separated out and neutralised with 5 M NaOH solution. The precipitate was filtered out and recrystallized from EtOH to give 2.56 g of **1** in 85% yield, white needles, mp 179-180 ºC. IR (cm^{-1}): 3074, 2966, 2936 (C-H); 1604, 1576, 1458 (C=C, C=N). ^{1}H NMR, δ (ppm), *J* (Hz): 2.06, s, 3H (H12a); 2.61, s, 3H (H2a); 4.00, s, 6H (H5a and H6a); 7.50, d, *J* 9, 1H (H3); 7.92, s, 1H (H7); 8.42, d, *J* 9, 1H (H4). ^{13}C NMR (assigned according to the HMBC spectrum) δ (ppm): 9.4 (C12a); 24.7 (C2a); 57.0 (C6a); 61.2 (C5a); 114.9 (C12); 119.8 (C8); 120.3 (C7); 121.6 (C10); 123.0 (C3); 130.4 (C4); 140.3 (C9); 144.4 (C5); 147.1 (C6); 157.8 (C11); 157.9 (C2). ESI HRMS, *m/z* (au)/relative intensity (%): 302.1132/100 ($M+H^+$); Calcd. for $C_{15}H_{16}N_3O_4$, 302.11408 au.

Table 1. The ^{1}H NMR signals of **1a** – **d** and **2a** – **f**, δ (ppm), J (Hz)

Compd. Ar—	H2a H2b	H3 H4	H5a / H6a	H7 H12a	H14 H15	H16 H17	H18 H15a	Others
1a 	7.47 d, J = 16 7.99 d, J = 16	8.00 d, J = 9,0 8.57 d, J = 9,0	 4.07 s 4.05 s	 7.97 s 2.11 s	- - 8.02 d, J = 8.0	7.60 t, J = 8.0 7.77 t, J = 7.5	8.07 d, J = 8.0 -	-
1b 	7.60 d, J = 16.5 7.82 d, J = 16.5	7.89 d, J = 9,0 8.56 d, J = 9.0	 4.07 s 4.05 s	 7.97 s 2.12 s	8.50 s - -	8.19 d, J = 8.0 7.71 t, J = 8.0	8.16 dd, J = 8.0, 1.5 -	-
1c 	7.62 d, J = 16.5 7.80 d, J = 16.5	8.02 d, J = 9.0 8.57 d, J = 9.0	 4.08 s 4.06 s	 7.97 s 2.12 s	8.24 d, J = 9.0 7.98 d, J = 9.0	- - 7.98 d, J = 9.0	8.24 d, J = 9.0 -	-
1d 	7.62 d, J = 16.5 7.77 d, J = 16.5	8.01 d, J = 9.0 8.56 d, J = 9.0	 4.04 s 4.03 s	 7.98 s 2.10 s	7.89 d, J = 2.0 -	 - -	8.00 d, J = 2.0 3.98 s	2.35 s, (H16b)
2a 	7.43 d, J = 16 8.21 d, J = 16	8.29 d, J = 9.0 8.64 d, J = 9.0	 4.06 s 4.05 s	 8.06 s 2.09 s	8.12 d, J = 8.5 7.61 t, J = 8.5	7.72 t, J = 8.0 7.61 t, J = 8.5	8.12 d, J = 8.0 -	-
2b 	7.71 d, J = 16 7.80 d, J = 16	8.28 d, J = 9.0 8.61 d, J = 9.0	 4.06 s 4.05 s	 8.06 s 2.08 s	8.04 d, J = 8.0 7.41 d, J = 8.0	- 7.41 d, J = 8.0	8.04 d, J = 8.0 -	2.43 s (H16a) -
2c 	7.72 d, J = 15 8.10 d, J = 15	8.22 d, J = 8.5 8.61 d, J = 9.0	 4.08 s 4.07 s	 8.04 s 2.09 s	8.11 d, J = 8.5 7.65 d, J = 8.0	- 7.65 d, J = 8.0	8.11 d, J = 8.5 -	-

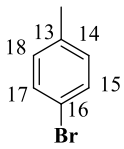
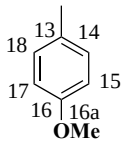
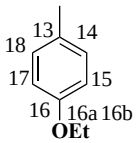
2d 	7.72 d, *J* = 15.5 8.18 d, *J* = 16	8.30 d, *J* = 8.5 8.61 d, *J* = 9.0	4.06 s 4.05 s	8.06 s 2.08 s	8.06 d, *J* = 8.5 7.81 d, *J* = 8.5	- 7.81 d, *J* = 8.5	8.06 d, *J* = 8.5 -	-
2e 	7.69 d, *J* = 15.5 8.22 d, *J* = 16	8.30 d, *J* = 8.5 8.61 d, *J* = 9.0	4.06 s 4.05 s	8.05 s 2.08 s	8.14 d, *J* = 8.5 7.12 d, *J* = 8.5	- 7.12 d, *J* = 8.5	8.14 d, *J* = 8.5 -	3.89 s (H16a) -
2f 	7.69 d, *J* = 15.5 8.22 d, *J* = 16	8.31 d, *J* = 8.5 8.61 d, *J* = 9.0	4.06 s 4.05 s	8.05 s 2.08 s	8.13 d, *J* = 8.5 7.10 d, *J* = 8.5	- 7.10 d, *J* = 8.5	8.13 d, *J* = 8.5 -	4.18 q, *J* = 7 1.38, *J* = 7

Table 2. The ^{13}C NMR signals of **1a** – **d**, δ (ppm)

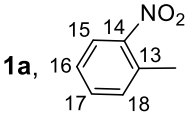
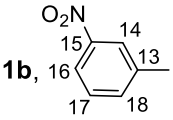
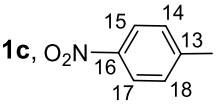
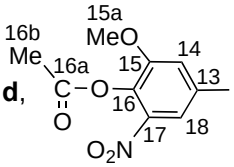
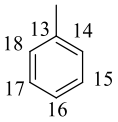
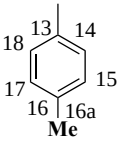
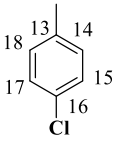
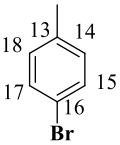
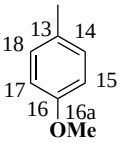
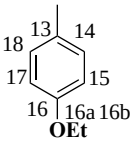
Compd., Ar—	**1a**, 	**1b**, 	**1c**, 	**1d**, 
C2, C3	153.2, 120.9	153.7, 120.1	153.4, 120.3	154.1, 120.5
C4, C5	130.9, 144.3	130.6, 144.3	130.6, 144.4	130.9, 144.3
C6, C7	147.6, 121.2	147.5, 121.0	147.5, 121.2	147.9, 120.9
C8, C9	120.4, 140.5	120.3, 140.5	120.1, 140.5	120.2, 140.6
C10, C11	122.5, 157.2	122.3, 157.2	122.4, 157.0	122.5, 157.6
C12, C12a	114.2, 8.8	114.4, 8.9	114.0, 8.8	115.3, 9.8
C5a, C6a	60.9, 57.0	60.9, 57.0	60.8, 57.0	61.2, 57.1
C2a, C2b	133.1, 128.3	121.4, 122.6	132.4, 131.9	115.0, 115.6
C13, C14	130.4, 148,0	137.8, 132.0	142.4, 127.8	142.4, 131.4
C15, C16	124.1, 129.2	148.2, 131.0	123.4, 146.8	142.8, 146.8
C17, C18	132.4, 128.2	129.9, 132.9	123.4, 127.8	152.6, 132.2
Others	-	-	-	56.9, 167.6, 20.1

Table 3. The ^{13}C NMR signals of **2a** – **f**, δ (ppm)

Compd. Ar—	**2a** 	**2b** 	**2c** 	**2d** 	**2e** 	**2f** 
C2, C3	152.3, 121.4	152.4, 121.4	152.3, 121.3	152.3, 121.3	152.3, 121.3	152.3, 121.3
C4, C5	131.2, 144.0	131.2, 144.1	131.2, 144.0	131.2, 144.0	130.9, 144.1	130.9, 144.1
C6, C7	148.5, 121.1	148.5, 121.1	148.6, 121.1	148.6, 121.1	148.0, 121.0	148.1, 121.1
C8, C9	120.9, 140.5	120.9, 140.5	121.0, 140.5	121.0, 140.5	120.7, 140.5	120.7, 140.5
C10, C11	123.3, 157.3	123.3, 157.3	123.3, 157.3	123.3, 157.3	123.0, 156.8	123.0, 156.9
C12, C12a	114.7, 9.2	114.8, 9.2	114.8, 9.2	114.8, 9.2	114.8, 9.2	114.3, 8.9
C5a, C6a	61.2, 57.0	61.2, 57.0	61.2, 57.0	61.2, 57.0	60.9, 57.0	60.7, 57.0
C2a, C2b	142.6, 127.4	141.2, 127.4	143.0, 127.2	143.0, 127.1	141.2, 127.4	141.3, 127.5
C2c, C13	189.3, 137.1	188.7, 134.6	188.4, 138.4	188.6, 136.1	187.3, 129.9	187.3, 129.8
C14, C18	128.9, 128.9	129.4, 129.4	130.5, 130.5	131.9, 131.9	128.9, 128.9	130.6, 130.6
C15, C17	128.5, 128.5	128.6, 128.6	129.0, 129.0	127.6, 127.6	128.9, 128.9	130.6, 130.6
C16, C16a	133.5, -	134.0, 21.1	135.8, -	130.5, -	163.2, 55.3	162.6, 63.4
C16b	-	-	-	-	-	14.1

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carbaldehyde (2). To a solution of **1** (1.506 g, 5 mmol) in dioxane (15 mL) at 60 ºC SeO_2 (0.555 g, 5 mmol) was added. The reaction mixture was stirred for 4 h at 80 ºC and then allowed to cool to room temperature. The resulting precipitate was filtered out and recrystallized from EtOH (using hot filter funnel to remove Se) to give 1.229 g of **2** in 78% yield, light yellow needles, mp 219-220 ºC. IR (cm^{-1}): 3050, 2950, 2851 (C-H); 1718 (C=O), 1613, 1586, 1477 (C=C, C=N). ^{1}H NMR, δ (ppm), *J* (Hz): 2.11, s, 3H (H12a); 4.05, s, 3H (H6a); 4.09, s, 3H (H5a); 8.05, d, *J* 9, 1H (H3); 8.18, s, 1H (H7); 8.74, d, *J* 9, 1H (H4); 10.02, s, 1H (H2a). ^{13}C NMR (assigned according to the HMBC spectrum), δ (ppm): 9.3 (C12a); 57.1 (C6a); 61.3 (C5a); 115.3 (C12); 117.8 (C3); 121.7 (C7); 121.9 (C8); 125.2 (C10); 132.2 (C4); 139.9 (C9); 143.2 (C5); 149.8 (C6); 150.9 (C2); 157.0 (C11); 193.3 (C2a). ESI HRMS, *m/z* (au)/relative intensity (%): 316.0922/10 ($M+H^+$), 338.0733/100 ($M+Na^+$); Calcd. for $C_{15}H_{14}N_3O_5$, 316.09335 au, for $C_{15}H_{13}N_3NaO_5$, 338.07529 au.

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carboxylic acid (3). To a solution of **1** (0.301 g, 1 mmol) in dioxane (4 mL) at 60 ºC SeO_2 (0.233 g, 2.1 mmol) was added. The reaction mixture was stirred

for 4 h at 100 ºC and then allowed to cool to room temperature. The resulting precipitate was filtered out and recrystallized from dioxane (using hot filter funnel procedure to remove Se) to give 0.248 g of **3** in 75% yield, yellow needles, mp 250-251 ºC. IR (cm^{-1}): 3250 (OH); 3030, 2957, 2851 (C-H); 1698 (C=O), 1612, 1550, 1473 (C=C, C=N). ^{1}H NMR, δ (ppm), *J* (Hz): 2.14, s, 3H (H12a); 4.06, s, 3H (H6a); 4.09, s, 3H (H5a); 8.14, s, 1H (H7); 8.19, d, *J* 9, 1H (H3); 8.70, d, *J* 9, 1H (H4). ^{13}C NMR, δ (ppm): 9.3 (C12a); 57.1 (C6a); 61.3 (C5a); 115.3 (C12); 121.4 (C3); 121.5 (C7); 121.8 (C8); 124.4 (C10); 131.9 (C4); 139.6 (C9); 143.9 (C5); 147.1 (C6); 149.2 (C2); 157.3 (C11); 165.8 (C2a). ESI HRMS, *m/z* (au)/relative intensity (%): 330.0739/100 ($M-H^+$); Calcd. for $C_{15}H_{12}N_3O_6$, 330.07261 au.

General procedure for the preparation of alkenes 1a – d.

Compound **1** (0.301 g, 1 mmol), a nitrobenzaldehyde (1 mmol), acetic anhydride (3 mL) and acetic acid (2 drops) was heated at 100 ºC for 5 h. After cooling down to room temperature, the precipitate was filtered out, washed with acetone, then Et_2O and recrystallized from toluene to give yellow crystals, the yield 60-75%.

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-(2-nitrostyryl)quinoline (1a). dark yellow needles, the yield 67%, mp 224-225 ºC. IR (cm^{-1}): 3078, 3004, 2949, 2846 (C-H); 1614, 1520, 1469 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 2. ESI HRMS, *m/z* (au)/relative intensity (%): 435.1295/100 ($M+H^+$); Calcd. for $C_{22}H_{19}N_4O_6$, 435.13046 au.

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-(3-nitrostyryl)quinoline (1b). yellow needles, the yield 65%, mp 217-218 ºC. IR (cm^{-1}): 3082, 3008, 2922, 2851 (C-H); 1616, 1529, 1471 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 2. ESI HRMS, *m/z* (au)/relative intensity (%): 435.1291/100 ($M+H^+$); Calcd. for $C_{22}H_{19}N_4O_6$, 435.13046 au.

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-(4-nitrostyryl)quinoline (1c). dark yellow crystals, the yield 75%, mp 278-280 ºC. IR (cm^{-1}): 3050, 2951, 2838 (C-H) ; 1615, 1592, 1520, 1471 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 2. ESI HRMS, *m/z* (au)/relative intensity (%): 435.1289/100 ($M+H^+$); Calcd. for $C_{22}H_{19}N_4O_6$, 435.13046 au.

5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-(4-acetoxy-3-methoxy-5-nitrostyryl)quinoline (1d). dark yellow needles, the yield 60%, mp 220-221 ºC. IR (cm^{-1}): 3096, 2948, 2851 (C-H); 1618, 1590, 1541, 1474 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 2. ESI HRMS, *m/z* (au)/relative intensity (%): 523.1443/100 ($M+H^+$); Calcd. for $C_{25}H_{23}N_4O_9$, 523.14650 au.

General procedure for the preparation of α,β-unsaturated ketones 2a – f.

Compound **2** (0.315 g, 1 mmol), a methyl phenyl ketone (1 mmol), EtOH (7 mL) and aqueous 50% KOH solution (5 drops) were stirred at room temperature for 2-3 h until numerous yellow solids appeared. Water (30 mL) was added to the resulting mixture, the precipitate was filtered out, washed with water to neutral medium, and then washed with EtOH. Recrystallize in a suitable solvent. The yield 70-80%.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-phenylprop-2-enone (2a). yellow needles, the yield 73%, mp 217-218 ºC. IR (cm^{-1}): 3000, 2945, 2848 (C-H); 1666 (C=O); 1608, 1593, 1550, 1471 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 418.1390/77 ($M+H^+$), 440.1210/100 ($M+Na^+$); Calcd. for $C_{23}H_{20}N_3O_5$, 418.14030 au.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-(4-methylphenyl)prop-2-enone (2b). light yellow needles, the yield 75%, mp 202-203 ºC. IR (cm^{-1}): 3010, 2951, 2851 (C-H); 1666 (C=O); 1611, 1591, 1540, 1470 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 432.1580/100 ($M+H^+$); Calcd. for $C_{24}H_{22}N_3O_5$, 432.15595 au.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-(4-chlorophenyl)prop-2-enone (2c). light yellow needles, the yield 70%, mp 220-222 ºC. IR (cm^{-1}): 3015, 2950, 2847 (C-H); 1666 (C=O); 1611, 1592, 1472 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 452.0997/100 ($M+H^+$), 474.0815/82 ($M+Na^+$); Calcd. for $C_{23}H_{19}ClN_3O_5$, 452.10132 au, for $C_{23}H_{18}ClN_3NaO_5$, 474.08327 au.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-(4-bromophenyl)prop-2-enone (2d). yellow needles, the yield 71%, mp 225-226 ºC. IR (cm^{-1}): 3010, 2941, 2845 (C-H); 1669 (C=O); 1610, 1592, 1469 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 496.0525/100 ($M+H^+$) and 498.0468/96 ($M+H^+$); Calcd. for $C_{23}H_{19}BrN_3O_5$, 496.05081 and 498.04876 au.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-(4-methoxyphenyl)prop-2-enone (2e). yellow needles, the yield 80%, mp 230-231 ºC. IR (cm^{-1}): 3000, 2945, 2845 (C-H); 1667 (C=O); 1600, 1590, 1470 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 448.1487/100 ($M+H^+$); Calcd. for $C_{24}H_{22}N_3O_6$, 448.15086 au.

(*E*)-3-[5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinolin-2-yl]-1-(4-ethoxyphenyl)prop-2-enone (2f). yellow needles, the yield 76%, mp 251-252 ºC. IR (cm^{-1}): 3009, 2987, 2846 (C-H); 1663 (C=O); 1610, 1591, 1471 (C=C, C=N). ^{1}H NMR and ^{13}C NMR see Table 1 and 3. ESI HRMS, *m/z* (au)/relative intensity (%): 462.1641/100 ($M+H^+$); Calcd. for $C_{25}H_{24}N_3O_6$, 462.16651 au.

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