Electronic supplementary materials *Mendeleev Commun*., 2019, **29**, 135–137

Pericyclic reactions in the synthesis of new 5-aryl-5,6-dihydroquinolino[2,1-*b*]quinazolin-12-ones

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Analytical studies were carried out using equipment of the Center for Joint Use “Spectroscopy and Analysis of Organic Compounds” at the I. Ya. Postovsky Institute of Organic Synthesis of the Russian Academy of Sciences (Ural Branch).

IR spectra were recorded on a Perkin Elmer Spectrum One IR Fourier transform spectrometer using a diffuse reflectance sampling accessory (DRA). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE-500 (500 and 126 MHz) spectrometer in DMSO-d_6, using TMS and DMSO-d_6 (δ_C 39.5 ppm) as references. ^{1}H and ^{13}C NMR signals were assigned using 2D ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and HMBC experiments. Electrospray ion mass spectra are recorded for positive polarity ions on an ultra-high resolution mass spectrometer qTOF maXis Impact HD (Bruker Daltonics, USA) with a standard ionization source in the mass range 50-2500 Da by injection analysis for solutions of samples in acetonitrile using a syringe pump input (model No. 601553 kdScientific Inc., USA); solution delivery rate 240 μl h^{-1}) in the modified pre-installed method "Direct_Infusion 100-1000". The calibration of the mass scale is external, according to the signals of a solution of lithium acetate by HPC methods or an improved quadratic one. All data is collected and processed in the software package Compass for oTof series 1.7 (oTOF Control 3.4; Bruker Compass Data Analysis 4.2). Melting points were measured on a Boetius heating microstage. Elemental analysis was performed on a Carlo Erba EA 1108 CHN-analyzer. Thin layer chromatography (UV-TLC) was carried out on Silufol UV-254 plates. Spots were visualized under the light of a low-pressure mercury lamp (6 W) or in iodine vapors. Column chromatography was performed over silica gel (Merck, 230–400 mesh).

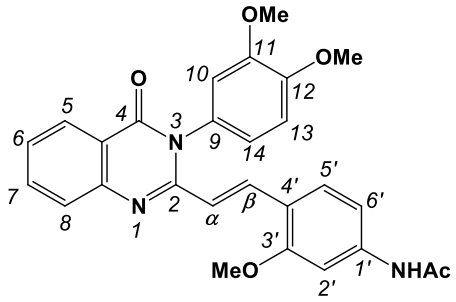
3-(3,4-Dimethoxyphenyl)-2-methylquinazolin-4(3H)-one (**1a**) and *2-methyl-3-(2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)quinazolin-4(3H)-one* (**1b**) were prepared by the earlier reported protocol [S1].

*5-Phenyl-5,6-dihydroquinolino[2,1-b]quinazolin-12-ones **2a,b** (general procedure)*. 4-Acetamido-2-methoxybenzaldehyde (0.52 or 0.37 mmol) and an equimolar amount of H_3BO_3 (0.5or 0.35 mmol) were added to a solution of compound **1a** or **1b** (0.15 g, 0.5 or 0.35 mmol) in acetic acid (30 ml). The mixture was refluxed in a brown glass flask for 180 h. After completion of the reaction, the solvent was evaporated, and the product was separated from impurities by column chromatography (SiO_2, eluent THF—hexane, 1:2). The target product was crystallized from acetonitrile.

N-[4-(2,3-Dimethoxy-12-oxo-5,6-dihydroquinolino[2,1-b]quinazolin-5-yl)-3-methoxyphenyl]-acetamide **2a**: yield 0.13 g (54%), m.p. 247-249 °C. ^{1}H NMR, δ: 1.96 (s, 3 H, C(1')NHCO*Me*), 3.26 (dd, 1 H, H(6B), *J* 15.6, 5.4 Hz), 3.29 (dd, 1 H, H(6A), *J* 15.6, 4.5 Hz), 3.74 (s, 3 H, C(3)O*Me*), 3.80 (s, 3 H, C(2)O*Me*), 3.84 (s, 3 H, C(3')O*Me*), 4.52 (t, 1 H, H(5), *J* 4.7 Hz), 6.44 (d, 1 H, H(5'), *J* 8.3 Hz), 6.79 (dd, 1 H, H(6'), *J* 8.3, 1.9 Hz), 6.89 (s, 1 H, H(4)), 7.40 (d, 1 H, H(2'), *J* 1.9 Hz), 7.48 – 7.53 (m, 2 H, H(8), H(10)), 7.77 (ddd, 1 H, H(9), *J* 8.2, 7.1, 1.4 Hz), 7.85 (s, 1 H, H^1), 8.19 (dd, 1 H, H(11), *J* 8.0, 1.4 Hz), 9.85 (s, 1 H, NH). ^{13}C NMR, δ: 23.87 (C(1')NHC(O)*Me*), 34.70 (C(5)), 38.51 (C(6)), 55.29 (C(3')O*Me*), 55.64 (C(3)O*Me*), 55.80 (C(2)O*Me*), 102.43 (C(2')), 108.74 (C(1)), 110.41 (C(6')), 110.82 (C(4)), 121.17 (C(11a)), 121.83 (C(4')), 125.86 (C(4a)), 126.33 (C(8)), 126.55 (C(10)), 126.75 (C(11)), 127.04 (C(5')), 127.39 (C(13a)), 134.50 (C(9)), 139.51 (C(1')), 145.78 (C(7a)), 146.59 (C(2)), 147.47 (C(3)), 153.43 (C(6a)), 156.62 (C(3')), 159.76 (C(12)), 168.13 (C(1')NH*C*(O)). IR (DRA, cm^{-1}): 3383, 3246, 3184, 3110, 3042, 2998, 2938, 2835, 1678, 1602, 1536, 1514, 1464, 1450, 1408, 1354, 1320, 1254, 1216, 1182, 1151, 1111, 1081, 1039, 956, 859, 772, 703, 648. HRMS (ESI), *m*/*z*: 472.1868 $[M + H]^+$ (calc. for $C_{27}H_{26}N_3O_5^+$, *m*/*z*: 472.1867). Found (%): C, 68.79; H, 5.32; N, 8.93. Calc. for $C_{27}H_{25}N_3O_5$ (%): C, 68.78; H, 5.34; N, 8.91.

N-[3-Methoxy-4-(22-oxo-2,3,5,6,8,9,11,12,16,22-decahydro-15H-[1,4,7,10,13]pentaoxacyclo-pentadecino[2',3':6,7]quinolino[2,1-b]quinazolin-15-yl)phenyl]acetamide **2b**: yield 0.1 g (51%), m.p. 237-239 °C. ^{1}H NMR, δ: 1.96 (s, 3 H, C(1')NHCO*Me*), 3.26 (dd, 1 H, H(16B), *J* 15.3, 5.1 Hz), 3.30 (dd, 1 H, H(16A), *J* 15.3, 4.4 Hz), 3.62 (m, 4 H, 2*O*CH*$_2$), 3.62 – 3.65 (m, 4 H, 2*O*CH*$_2$), 3.74 (m, 2 H, O*CH*$_2$), 3.81 (m, 2 H, O*CH*$_2$), 3.84 (s, 3 H, C(3')O*Me*), 3.96 – 4.07 (m, 2 H, O*CH*$_2$), 4.09 (m, 2 H, O*CH*$_2$), 4.50 (t, 1 H, H(15), *J* 4.8 Hz), 6.46 (d, 1 H, H(5'), *J* 8.3 Hz), 6.80 (dd, 1 H, H(6'), *J* 8.3, 1.9 Hz), 6.85 (s, 1 H, H(14)), 7.41 (d, 1 H, H(2'), *J* 1.9 Hz), 7.48 – 7.53 (m, 2 H, H(18), H(20)), 7.77 (ddd, 1 H, H(19), *J* 8.2, 7.0, 1.4 Hz), 7.82 (s, 1 H, H(24)), 8.18 (dd, 1 H, H(21), *J* 8.0, 1.4 Hz), 9.86 (s, 1 H, NH). ^{13}C NMR, δ: 23.87 (C(1')NHC(O)*Me*), 34.68 (C(15)), 38.48 (C(16)), 55.29 (C(3')O*Me*), 68.55, 68.66, 68.74, 69.05, 69.72, 69.80, 70.37 and 70.42 (8*OCH$_2$), 102.42 (C(2')), 110.43 (C(6')), 110.75 (C(24)), 112.44 (C(14)), 121.17 (C(21a)), 121.81 (C(4')), 126.33 (C(18)), 126.37 (C(14a)), 126.54 (C(20)), 126.73 (C(21)),

127.07 (C(5')), 127.46 (C(23a)), 134.50 (C(19)), 139.52 (C(1')), 145.78 (C(17a)), 146.31 (C(24a)), 147.28 (C(13a)), 153.44 (C(16a)), 156.64 (C(3')), 159.73 (C(22)), 168.12 (C(1')NH*C*(O)Me). IR (DRA, cm^{-1}): 3245, 3183, 3107, 3040, 2936, 2870, 1681, 1603, 1541, 1511, 1466, 1451, 1428, 1408, 1353, 1320, 1285, 1256, 1217, 1182, 1141, 1113, 1085, 1060, 1039, 1012, 986, 932, 857, 769, 694. HRMS (ESI), *m*/*z*: 602.2496 $[M + H]^+$ (calc. for $C_{33}H_{36}N_3O_8^+$, *m*/*z*: 602.2497). Found (%): C, 65.90; H, 5.84; N, 6.99. Calc. for $C_{33}H_{35}N_3O_8$ (%): C, 65.88; H, 5.86; N, 6.98.



2-[(E)-2-(4-Acetamido-2-methoxyphenyl)vinyl]-3-(3,4-dimethoxyphenyl)quinazolin-4(3H)-one (**A**) was obtained similarly, but the reaction mixture was refluxed in a brown glass flask for ~35 h. The solvent was evaporated, and the intermediate **A** was separated from the reactants and product **2a** by column chromatography (SiO_2, 2-propanol—hexane 1:4) and finally crystallized from EtOH. Yield 0.05 g, m.p. 284-285 °C. ^{1}H NMR (DMSO-d_6) δ/ppm: 2.04 (s, 3H, C(1')NHC(O)*Me*), 3.66 (s, 3H, C(3')O*Me*), 3.75 (s, 3H, C(11)O*Me*), 3.87 (s, 3H, C(12)O*Me*), 6.56 (d, 1H, H(α), *J* 15.6 Hz), 6.94 (dd, 1H, H(14), *J* 8.5, 2.3 Hz), 7.10 (d, 1H, H(10), *J* 2.3 Hz), 7.12 (dd, 1H, H(6'), *J* 8.5, 1.4 Hz), 7.14 (d, 1H, H(5'), *J* 8.5 Hz), 7.24 (d, 1H, H(13), *J* 8.5 Hz), 7.39 (d, 1H, H(2'), *J* 1.4 Hz), 7.49 (ddd, 1H, H(6), *J* 8.1, 7.0, 0.8 Hz), 7.74 (d, 1H, H(8), *J* 8.0 Hz), 7.84 (ddd, 1H, H(7), *J* 8.0, 7.0, 1.3 Hz), 7.96 (d, 1H, H(β), *J* = 15.6 Hz), 8.11 (dd, 1H, H(5), *J* 8.1, 1.3 Hz), 10.13 (s, 1H, NH). ^{13}C NMR (151 MHz, DMSO-d_6) δ/ppm: 24.64, 55.47, 56.23, 56.31, 102.39, 111.60, 112.32, 113.03, 118.72, 119.59, 120.89, 121.44, 126.59, 126.90, 127.36, 130.31, 130.65, 135.07, 135.11, 142.57, 147.88, 149.49, 149.81, 153.31, 158.85, 161.95, 169.15. IR (DRA, cm^{-1}): 3304, 3271, 3185, 3076, 2926, 2853, 1674, 1596, 1532, 1511, 1464, 1408, 1317, 1264, 1249, 1173, 1136, 1117, 1024, 841, 778, 767, 698. Found (%): C, 68.74; H, 5.36; N, 8.89. Calc. for $C_{27}H_{25}N_3O_5$ (%): C, 68.78; H, 5.34; N, 8.91.

Computational procedure. All of the structures were optimized in the gas phase using Orca 4.0.1 program complex with Restricted Hartree-Fock theory calculations and the 3-21G and 6-311G* basis sets [S2-S5]. The optimized structures **B**, **C**, **D** and **E** were proofed by the absence of imaginary frequencies in Hessian, and the **TS** and **TS**-**D**/**E** – by the presence of one imaginary frequency.

Table S1. The values of relative energies, distance *r* between C(β) and C(14) reaction centers and torsion angles of the intermediate and transition state structures obtained with the 3-21G and 6-311G* basis sets for the disrotatory electrocyclization of *E*-styrylquinazolinone and the following [1,5]-hydrogen shift.

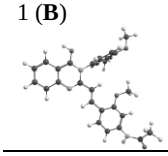
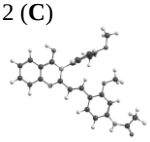
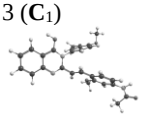
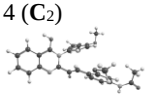
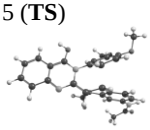
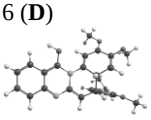
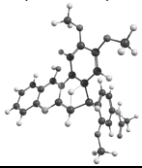
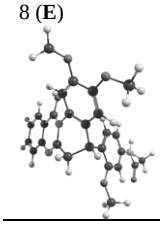
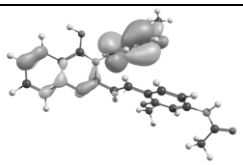
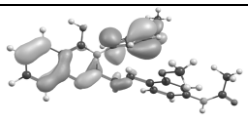
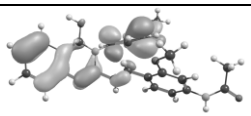
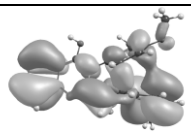
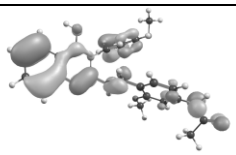
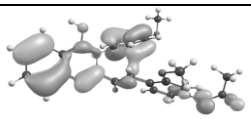
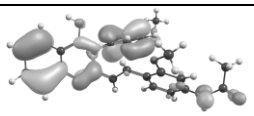
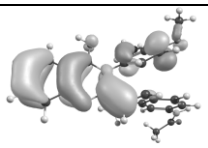
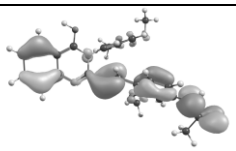
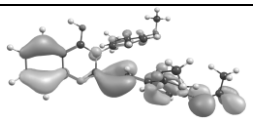
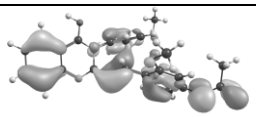
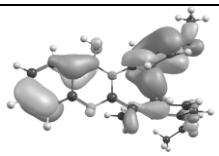
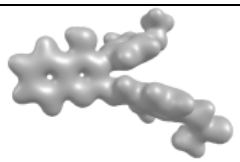
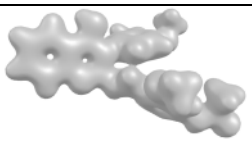
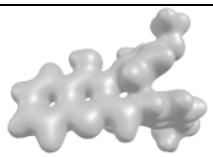
Reaction coordinate (intermediate)	Distance, *r* (Å)	Basis set					
		RHF/3-21G			RHF/6-311G*		
		E_a, kcal mol^{-1}	Torsion angles, (deg)		E_a, kcal mol^{-1}	Torsion angles, (deg)	
			N_3-C_2-C_α-C_β; C_{14}-C_9-N_3-C_2	C_2-C_α-C_β-H_β; N_3-C_9-C_{14}-H_{14}		N_3-C_2-C_α-C_β; C_{14}-C_9-N_3-C_2	C_2-C_α-C_β-H_β; N_3-C_9-C_{14}-H_{14}
1 (**B**) 	4.7	0	-179.550 -89.253	0.254 -2.308	0	-179.577 -89.918	0.058 -1.061
2 (**C**) 	3.4	7.39344	-6.157 -101.876	2.006 -0.585	5.736054	-0.595 -90.097	-0.646 -0.014
3 (**C**$_1$) 	2.6	25.76526	59.666 -79.505	11.750 -14.726	25.16705	55.82 -80.24	11.750 -15.614
4 (**C**$_2$) 	2.4	32.88747	55.231 -75.904	16.939 -20.450	35.00131	50.49 -76.97	19.462 -21.869
5 (**TS**) 	2.0	66.39869	-3.435 -46.598	133.057 -25.103	68.35987	0.31 -46.72	125.169 -24.581
6 (**D**) 	1.6	49.76549	4.992 -25.283	135.134 -61.658	51.13068	4.130 -29.232	132.134 -58.707
7 (**TS**-**D**/**E**) 	$r_{C(4a)-H(4a)}$/$r_{C(6)-H(4a)}$ 1.35/1.62	70.49921			73.41078		
8 (**E**) 		-16.5778			-12.38177		

Table S2. The energy levels of the frontier molecular orbitals of intermediates **C**$_{1\text{-}3}$ and **TS**, which were estimated by RHF/6-311G*. The distance between terminal carbon atoms in pseudocyclic intermediates varies from 2.6 to 2.0 Å.

Energy level	Structure (*r*, Å)			
	C_1 (2.6 Å)	C_2 (2.4 Å)	C_3 (2.1 Å)	TS (2.0 Å)
HOMO-3				
HOMO-4				
HOMO-5				
Total SCF Density				

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