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MODIFICATION OF THE PICTET–SPENGLER REACTION IN THE SYNTHESIS OF FUSED 2,3-BENZODIAZOCINES

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A new strategy for the synthesis of the eight-membered heterocyclic skeleton of tetrahydroquinazolino[3,2-c][2,3]benzodiazocin-15-ones, based on the Pictet–Spengler reaction of 3-amino-2-[2-(3,4-dimethoxyphenyl)ethyl]quinazolin-4(3H)-one with carbonyl compounds in acidic media, is proposed.

Keywords: 3-amino-2-[2-(3,4-dimethoxyphenyl)ethyl]quinazolin-4(3*H*)-one, fused diazocines, hydrochloric acid, tetrahydroquinazolino[3,2-*c*][2,3]benzodiazocin-15-ones, trifluoroacetic acid, cyclization, Pictet–Spengler reaction.

2,3-Benzodiazocines are homologs of 2,3-benzodiazepines. Methods used for preparation of benzodiazepines have been well-developed [1], while benzodiazocines are still not readily available. Only a few examples for the synthesis of benzodiazocines have been described in the literature, by intramolecular aziridation of the double bond in 3-aminoquinazolone under the action of lead tetraacetate [2-6], and also by cyclization of *ortho*-phenylenedicarbonyl compounds by the action of hydrazine hydrobromide [7-9].

Recently, we reported the synthesis of heteroannellated 2,3-benzodiazepines using the Pictet–Spengler reaction from 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3*H*)-one and carbonyl compounds in hydrochloric or trifluoroacetic acids [10,11]. This method was also used for the synthesis of benzothienodiazepines [12].

With the aim of determining the limits of application of the Pictet–Spengler reaction, we investigated the possibility of obtaining the eight-membered heterocyclic skeleton of 9,10-dimethoxy-6,7,12,13-tetrahydro-15*H*-quinazolino[3,2-*c*][2,3]benzodiazocin-15-ones **2** by the reaction of 3-amino-2-[2-(3,4-dimethoxyphenyl)-ethyl]quinazolin-4(3*H*)-one (**1**) with carbonyl compounds in acidic media.

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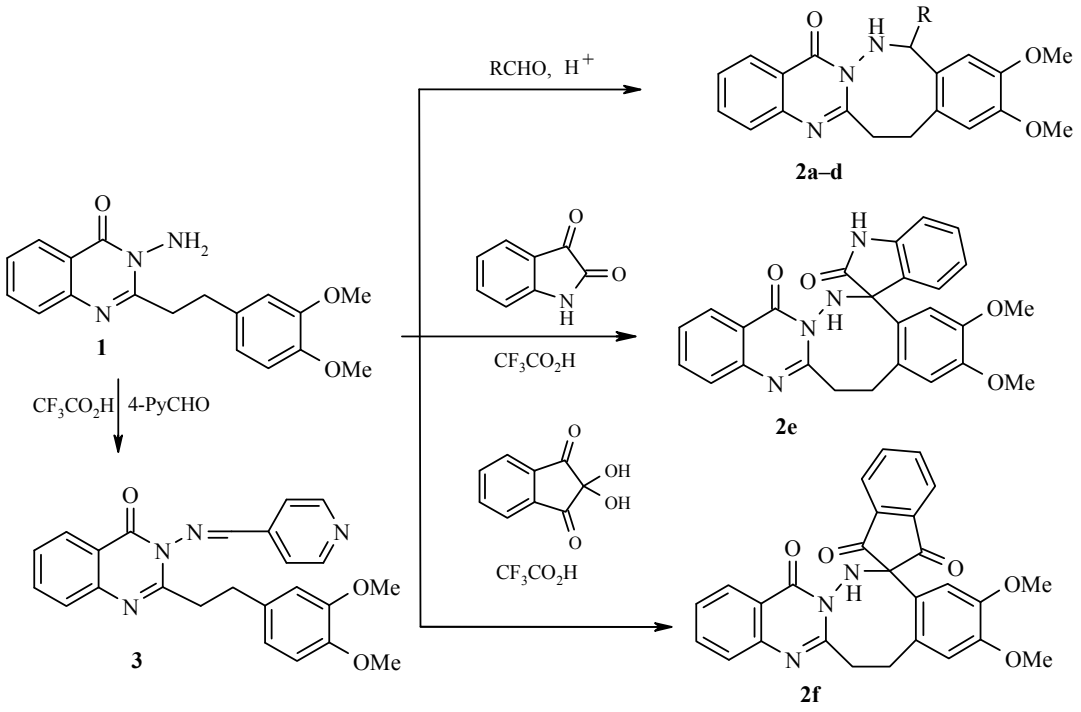
We showed previously that in the synthesis of benzodiazepines the best yields were obtained using hydrochloric acid as the cyclizing agent [10, 11]. While studying the reaction of formation of diazocines **2a-f**, we discovered that compound **1** in hydrochloric acid reacts well only with paraformaldehyde. The corresponding diazocine **2a** was isolated as the hydrochloride in 87% yield. Reaction with benzaldehydes and 4-pyridinecarboxaldehyde in hydrochloric acid gave low yields of diazocines **2b-d**, while isatin and ninhydrin did not react at all. In trifluoroacetic acid, amine **1** interacts with benzaldehydes, isatin, and ninhydrin, forming the corresponding 12-substituted benzodiazocines **2b,c,e,f** in 35-70% yield (Table 1). However, the reaction with 4-pyridinecarboxaldehyde in trifluoroacetic acid stopped at the stage of formation of azomethine **3**. Aliphatic aldehydes and pyruvic acid ethyl ester did not react at all.



2 a R = H, **b** R = 4-MeC_6H_4, **c** R = 4-ClC_6H_4, **d** R = 4-Py

It was discovered that under identical conditions the formation of diazocines occurred significantly more slowly than diazepines. For example, completion of the reaction of compound **1** with aromatic aldehydes in trifluoroacetic acid required no less than 48 h, while diazepines were usually formed in 6-8 h [10, 11].

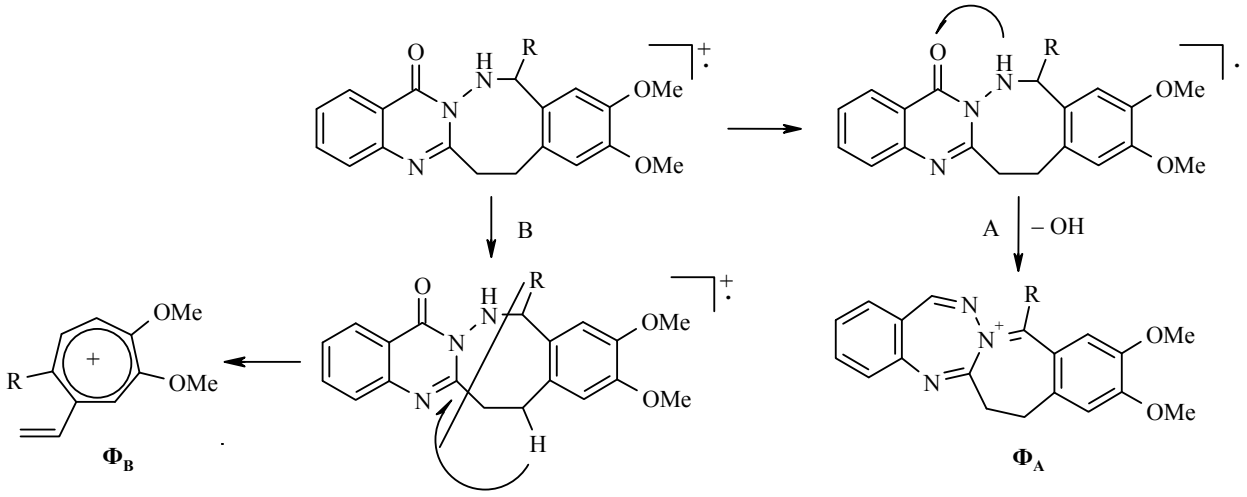
On heating amine **1** with benzaldehydes in CF_3COOH for 24 h, up to 50% Schiff's base was present in the reaction mixture, which is possibly connected with spatial factors (with the large distance from the azomethine carbon atom to the C(6) atom of the veratrole ring). It is also possible that the low yields of compounds **2b-d** in hydrochloric acid are due to the competing reaction of hydrolysis of the Schiff's base. On carrying out the cyclization in hydrochloric acid diazocines **2b-d** were isolated in 10-15% yields.

To confirm the structure of compounds obtained, mass spectra with ionization by electron impact were recorded (Table 2). As it should be seen from the data given, the molecular ion peaks of compounds **2b** and **2c** were of low intensity, which reduces the reliability of identifying them. Consequently, to confirm their structure, mass spectra were recorded using ionization by fast atom bombardment (FAB) in which $[M+H]^+$ ion peaks of maximum intensity were observed. Irrespective of the method of ionization, the mass spectra of compounds **2b** and **2c** were characterized by identical fragment ions. On the basis of the spectra of metastable ions (B/E and B^2/E linked scanning), two main mutually competing directions for the fragmentation A and B can be distinguished.

TABLE 1. Characteristics of Compounds Synthesized **1-3**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	Cl	N		
1	$C_{18}H_{19}N_3O_3$	66.58 / 66.45	5.76 / 5.89	—	12.95 / 12.91	137	63
2a	$C_{19}H_{19}N_3O_3 \cdot HCl$	60.96 / 61.04	5.42 / 5.39	9.39 / 9.48	11.39 / 11.24	229	87*
2b	$C_{26}H_{25}N_3O_3$	73.18 / 73.05	5.96 / 5.89	—	9.79 / 9.83	155–156	40*[2]
2c	$C_{25}H_{22}ClN_3O_3$	67.21 / 67.04	5.12 / 4.95	7.95 / 7.91	9.21 / 9.38	187–189	35*[2]
2d	$C_{24}H_{22}N_4O_3$	69.67 / 69.55	5.56 / 5.35	—	13.63 / 13.52	208–209	10*
2e	$C_{26}H_{22}N_4O_4$	68.90 / 68.71	5.02 / 4.88	—	12.38 / 12.33	319–320	65*[2]
2f	$C_{27}H_{21}N_3O_5$	69.33 / 69.37	4.58 / 4.53	—	8.89 / 8.99	270 (decomp.)	70*[2]
3	$C_{24}H_{22}N_4O_3$	69.51 / 69.55	5.47 / 5.35	—	13.56 / 13.52	134–135	90

*Cyclizing agent hydrochloric acid.
*[2]Cyclizing agent trifluoroacetic acid.



Direction A, as is evident from the presented scheme, is connected with the elimination of a hydroxyl radical by the molecular ions and the formation of ions Φ_A $[M-17]^+$. Since such a fragment is absent from the molecules of the compounds being analyzed, it may be assumed that its formation is the result of migration of a hydrogen atom to the carbonyl group. It is probable that the source of such hydrogen atoms is the NH group of the neighboring eight-membered ring.

The second factor determining the stability of the molecular ions of compounds **2a-d** is the intensity of the fragmentation in direction B, which leads to the formation of ions Φ_B with a mass of 176+R. As is seen from the scheme, this is connected with the decomposition of the eight-membered ring, the ease of proceeding of which depends on the character of the substituent R. It is evident that electron-donating substituents must facilitate the stabilization of the cations formed, meaning, to increase the probability of their formation. Such a proposal is in agreement with the observed change in intensity of the peak of ions Φ_B in the mass spectra of compounds **2a-d**.

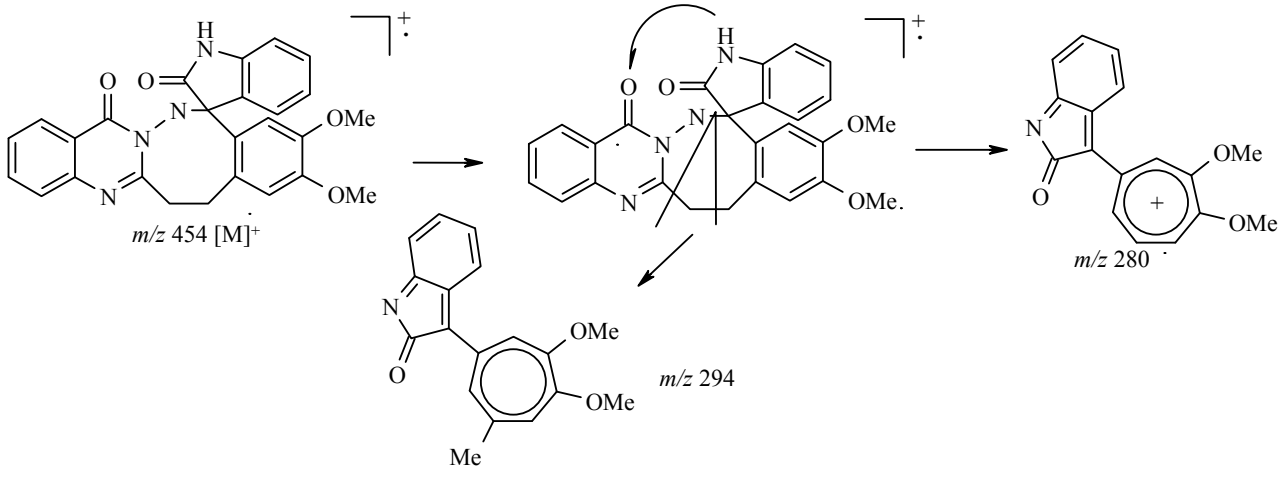
TABLE 2. Mass Spectra of Compounds **2a-f**

Compound	*m/z* (I_{rel} %)
2a	337 $[M]^+$ (34), 322 (21), 321 (30), 320 (100), 306 (22), 305 (57), 277 (10), 191 (2), 186 (11), 177 (19), 176 (18), 161 (13), 160 (17), 77 (13)
2b	427 $[M]^+$ (1), 411 (21), 410 (74), 395 (14), 268 (24), 267 (100), 252 (25)
2c	447 $[M]^+$ (2), 432 (35), 431 (36), 430 (100), 418 (11), 417 (17), 416 (31), 415 (29), 289 (34), 288 (36), 287 (94), 272 (26), 165 (13), 160 (14), 151 (18), 139 (19), 111 (11)
2d	414 $[M]^+$ (55), 397 (100), 382 (40), 336 (12), 267 (10), 254 (88), 239 (24), 160 (11), 151 (11)
2e	454 $[M]^+$ (100), 426 (13), 395 (18), 295 (10), 294 (47), 281 (19), 280 (68), 279 (24), 216 (11), 57 (12), 55 (10)
2f	467 $[M]^+$ (58), 334 (14), 320 (27), 308 (25), 307 (11), 293 (20), 132 (16), 105 (20), 104 (100), 76 (18)
2b*	428 $[M + H]^+$ (100), 427 (10), 426 (12), 411 (17), 410 (52), 268 (12), 267 (39)
2c*	448 $[M + H]^+$ (100), 447 (12), 446 (11), 432 (21), 431 (15), 430 (46), 289 (19), 288 (11), 287 (28)

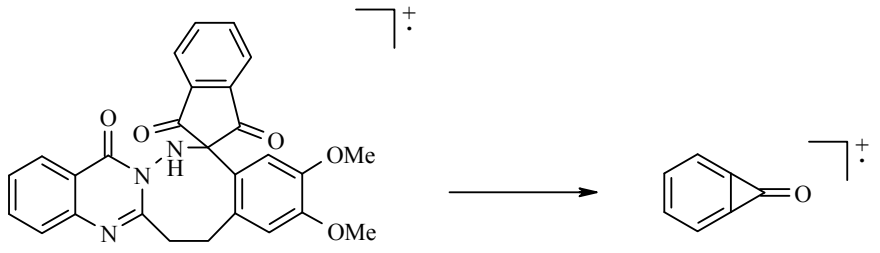
*FAB spectra.

For compound **2a,** the observed direction of decomposition is brought about to an insignificant extent by the absence of the stabilizing effect of a substituent on the stability of the resulting fragments. The result of this is the relatively low intensity of the $\mathbf{\Phi_B}$ ion peak (19%). The dominant direction of decomposition in this case is direction A (intensity of the peak of ions $\mathbf{\Phi_A}$ is 100%). Introduction of aromatic fragments as substituent R significantly increases the probability of carrying out decomposition by direction B, but the relative intensity of ion peaks $\mathbf{\Phi_B}$ is in good agreement with the electron-donating properties of substituent R. As follows from the data of Table 2 the ratio of intensities of ion peaks $\mathbf{\Phi_B}$ and $\mathbf{\Phi_A}$ for compound **2b** is 1.36, while for compound **2c** this value is 0.94, and for compound **2d** 0.88.

Introduction of an isatin fragment almost entirely suppressed the direction of decomposition connected with elimination of a hydroxyl radical and increased the stability of molecules towards electron impact. Low-intensity ion peaks were observed in the mass spectrum, formed as a result of the sequential elimination of a molecule of CO (*m/z* 426) and a methoxyl radical (*m/z* 395). The dominant direction of decomposition in this case was accompanied by cleavage of the eight-membered ring with the formation of fragment ions of *m/z* 294 and 280, which probably have the structure shown in the following scheme.



The direction of decomposition observed for compound **2f** is accompanied by complete elimination of the ninhydrin fragment and the formation of an ion of *m/z* 104, the peak of which was the maximum in the spectrum.



m/z 467 $[M]^+$ *m/z* 104

According to the data of X-ray diffraction study the eight-membered heterocycle has a *twist-boat* conformation (Fig. 1) The C(6)–C(7) and C(12)–N(13) bonds lying in the base of *boat* are twisted relative to one another by -20.2°. The C(5A), C(7), C(11), and N(14) atoms deviate from the mean square plane made through the atoms of the base by 1.17, 0.98, 1.10, and 0.99 Å respectively. The significant bend of this ring causes the formation of strong intramolecular shortened contacts: C(5A)···C(11A) 3.16 Å (sum of the van der Waals radii [13] 3.42 Å), N(14)···C(7A) 3.09 (3.21), N(13)···C(7) 2.80 (3.21), N(13)···H(7B) 2.53 Å (2.66 Å). The N(13) atom has a pyramidal configuration (sum of valence angles centered on the atom was 335°). The methoxy groups lay in the plane of the C(7A)–C(11A) benzene ring (the C(11)–C(10)–O(3)–C(17) and C(8)–C(9)–O(2)–C(16) torsion angles were -0.9(3)° and 9.6(3)° respectively), in spite of shortened contacts H(8)···H(16C) 2.29 (2.32) and H(11)···H(17B) 2.27 Å (2.32 Å).

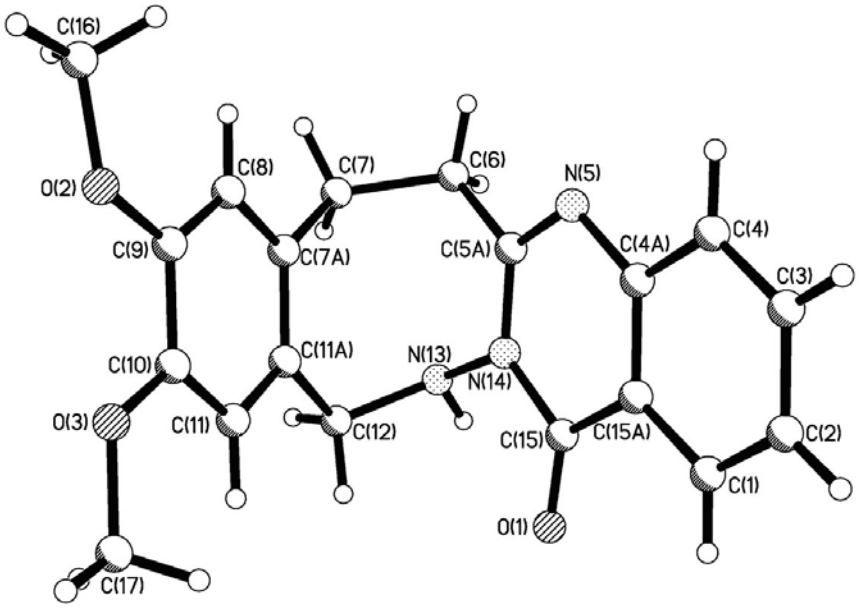


Fig. 1. Structure of the compound **2a** molecule according to X-ray structural analysis.

In the crystal the **2a** molecule is disordered in two orientations differing in the direction of the carbonyl group with populations 82:18%. This leads to the appearance of intermolecular shortened contacts C(2)···H(13') (2.5-*x*, 0.5+*y*, -0.5-*z*) 2.67, C(3)···H(13') (2.5-*x*, 0.5+*y*, -0.5-*z*) 2.76, C(3)···H(6'B') (2.5-*x*, 0.5+*y*, -0.5-*z*) 2.74 Å (sum of van der Waals radii [13] 2.87 Å); H(16C)···H(6'A') (-1+*x, y, z*) 2.13 Å (sum of van der Waals radii [13] 2.32 Å).

The X-ray structural investigation of 2a hydrochloride (Fig. 2) showed that salt formation led to the disappearance of disordering in the crystal. Protonation of the N(5) atom of the pyrimidine ring therefore occurs, which appears to be linked with chloride anion by a strong hydrogen bond N(5)–H(5)···Cl(1) (H···Cl 1.92 Å, N–H···Cl 171°).

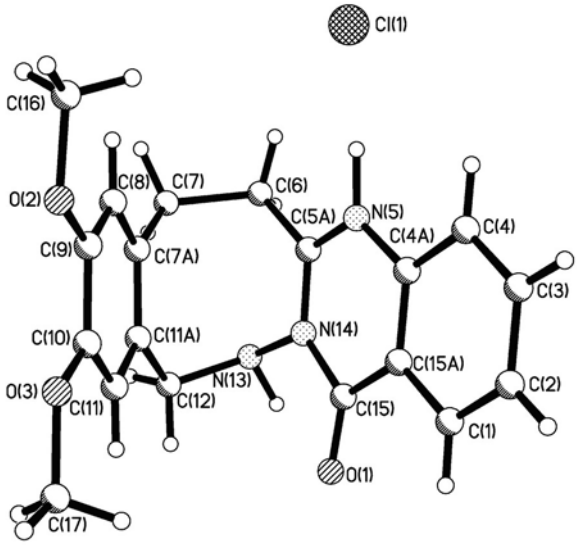


Fig. 2. Structure of compound **2a** hydrochloride according to data of X-ray structural analysis.

Salt formation has a weak influence on the conformation of the molecule. The twisting of bonds lying in the base of the *boat* conformation of the eight-membered ring is somewhat less than in the neutral molecule (-16.4°), but the deviation of the atoms from the mean square plane through the atoms of the base was somewhat greater (deviation of atoms C(5A), C(7), C(11), and N(14) were 1.19, 1.05, 1.15, and 1.06 Å respectively). Some increase was also observed in the pyramidality of the N(13) atom. The sum of the valence angles centered on the atom in the hydrochloride was 328°.

We have therefore shown that the Pictet–Spengler reaction may be used successfully not only for obtaining fused benzodiazepines [10, 11], but also for the previously unknown 9,10-dimethoxy-12-R-6,7,12,13-tetrahydro-15*H*-quinazolino[3,2-*c*][2,3]benzodiazocine-15-ones.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance II 400 (at 400 MHz) in DMSO-d_6 solution, internal standard was TMS. Electron ionization mass spectra were recorded on a MX 1321 mass spectrometer at an ionizing voltage of 70 eV, temperature of ionization chamber 220°C using direct insertion of sample. The spectra of metastable ions were recorded on a VG7070 mass spectrometer under the same conditions. The FAB spectra were recorded on the VG7070 mass spectrometer. Desorption of ions from sample solutions in *p*-nitrobenzyl alcohol was effected with a pulse of argon atoms with an energy of 8 keV.

Crystals of compound **2a** were monoclinic, $C_{19}H_{19}N_3O_3$, at 293 K, *a* 9.826(1) Å, *b* = 13.633(1) Å, *c* = 12.199(1) Å, β = 99.09(1)°, *V* = 1613.5(2) Å^3, M_r = 337.37, *Z* = 4, space group $P2_1/n$, d_{calc} = 1.389 g/cm^3, μ(MoKα) = 0.096 mm^{-1}, *F*(000) = 712. Parameters of the unit cell and the intensities of 9072 reflections (2655 independent, R_{int} = 0.052) were measured on a Xcalibur-3 diffractometer (MoKα radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 50°).

TABLE 3. ^{1}H NMR Spectra of Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	3.06 (2H, m, $ArCH_2$); 3.24 (2H, m, $HetarCH_2$); 3.76 (3H, s) and 3.78 (3H, s, 3',4'-OCH_3); 5.64 (2H, s, NH_2); 6.77 (1H, d, $J_{5',6'}$ = 8.0, H-5'); 6.81 (1H, d. d, $J_{6',5'}$ = 8.0, $J_{6',2'}$ =1.6, H-6'); 6.85 (1H, d, $J_{2',6'}$ = 1.6, H-2'); 7.42 (1H, t, *J* = 8.0, H-6); 7.60 (1H, d, *J* = 8.0, H-8); 7.71 (1H, t, *J* = 8.0, H-7); 8.13 (1H, d, *J* = 8.0, H-5)
2a	3.55 (2H, m, 7-CH_2); 3.69 (2H, m, 6-CH_2); 3.60 (3H, s) and 3.73 (3H, s, 9,10-OCH_3); 4.30 (1H, br. s, NH in exchange with H_2O); 4.41 (2H, s, 12-CH_2); 6.50 (1H, s, H-8); 6.78 (1H, s, H-11); 7.50 (1H, t, *J* = 8.0, H-2); 7.72-7.83 (2H, m, H-3,4); 8.20 (1H, d, *J* = 8.0, H-1)
2b	2.34 (3H, s, CH_3); 2.74 (1H, m) and 3.53 (1H, m, 7-CH_2); 3.10 (1H, m) and 3.95 (1H, m, 6-CH_2); 3.61 (3H, s) and 3.75 (3H, s, 9,10-OCH_3); 5.74 (1H, d, *J* = 3.2, 12-CH); 6.53 (1H, s, H-8); 6.65 (1H, d, *J* = 3.2, NH); 6.71 (1H, s, H-11); 7.13 (2H, d, *J* = 8.0, H-3',5'); 7.28 (2H, d, *J* = 8.0, H-2',6'); 7.38 (1H, t, *J* = 8.0, H-2); 7.43 (1H, d, *J* = 8.0, H-4); 7.65 (1H, t, *J* = 8.0, H-3); 8.10 (1H, d, *J* = 8.0, H-1)
2c	2.73 (1H, m) and 3.55 (1H, m, 7-CH_2); 3.09 (1H, m) and 3.81 (1H, m, 6-CH_2);
2d	2.71 (1H, m) and 3.59 (1H, m, 7-CH_2); 3.04 (1H, m) and 3.75 (1H, m, 6-CH_2); 3.66 (3H, s) and 3.74 (3H, s, 9,10-OCH_3); 5.85 (1H, d, *J* = 3.2, 12-CH); 6.69 (1H, s, H-8); 6.71 (1H, s, H-11); 7.24 (1H, d, *J* = 3.2, NH); 7.37 (1H, t, *J* = 8.0, H-2); 7.41 (2H, d, *J* = 4.8, H-3',5'); 7.44 (1H, d, *J* = 8.0, H-4); 7.65 (1H, t, *J* = 8.0, H-3); 8.09 (1H, d, *J* = 8.0, H-1); 8.49 (2H, d, *J* = 4.8, H-2',6')
2e	2.96 (1H, m) and 3.57 (1H, m, 7-CH_2); 3.31 (1H, m) and 4.73 (1H, m, 6-CH_2); 3.55 (3H, s) and 3.83 (3H, s, 9,10-OCH_3); 6.11 (1H, s, H-8); 6.70 (1H, s, H-11); 6.84 (1H, s, NH); 6.94 (1H, t, *J* = 7.6, H-6'); 7.00 (1H, d, *J* = 7.6, H-4'); 7.25 (1H, t, *J* = 7.6, H-5'); 7.29 (1H, d, *J* = 7.6, H-7'); 7.38 (1H, t, *J* = 8.0, H-2); 7.47 (1H, d, *J* = 8.0, H-4); 7.68 (1H, t, *J* = 8.0, H-3); 8.00 (1H, d, *J* = 8.0, H-1); 10.76 (1H, s, NH)
2f	2.92 (1H, m) and 3.55 (1H, m, 7-CH_2); 3.22 (1H, m) and 4.65 (1H, m, 6-CH_2); 3.45 (3H, s) and 3.82 (3H, s, 9,10-OCH_3); 5.97 (1H, s, H-8); 6.91 (1H, s, H-11); 7.40 (1H, t, *J* = 8.0, H-2); 7.46 (1H, d, *J* = 8.0, H-4); 7.69 (1H, t, *J* = 8.0, H-3); 8.01 (1H, d, *J* = 8.0, H-1); 8.03–8.15 (5H, m, H-4',5',6',7' + NH)
3	3.04 (2H, m, $ArCH_2$); 3.20 (2H, m, $HetarCH_2$); 3.66 (3H, s) and 3.75 (3H, s, 3',4'-OCH_3); 6.66–6.73 (3H, m, H-2',5',6'); 7.50 (1H, t, *J* = 8.0, H-6); 7.67 (1H, d, *J* = 8.0, H-8); 7.80 (1H, t, *J* = 8.0, H-7); 7.81 (2H, d, *J* = 5.2, H-3",5"); 8.20 (1H, d, *J* = 8.0, H-5); 8.75 (2H, d, *J* = 5.2, H-2",6"); 9.10 (1H, s, CH=N)

Crystals of compound **2a** hydrochloride were monoclinic, $C_{19}H_{20}ClN_3O_3$, at 293 K, a = 9.131(1), b = 14.817(4), c = 13.633(3) Å, β = 95.65(2)°, V = 1835.5(6) Å3, M_r = 373.83, Z = 4, space group $P2_1/n$, d_{calc} = 1.353 g/cm^3, μ(MoKα) = 0.232 mm^{-1}, F(000) = 784. Parameters of the unit cell and intensities of 12268 reflections (3181 independent, R_{int} = 0.074) were measured on a Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max} = 50^o$).

The structures were solved by the direct method using the SHELXTL package [14]. The positions of hydrogen atoms were located from an electron density difference maps and were refined using "rider" model with $U_{iso} = nU_{eq}$ of the non-hydrogen atom linked with the given hydrogen (n = 1.5 for methyl groups and n = 1.2 for the remaining hydrogen atoms). Structures were refined against F^2 by the full-matrix least-squares method in an anisotropic approximation for non-hydrogen atoms to wR_2 = 0.167 for 2655 reflections (R_1 = 0.068 at 1461 reflections with $F > 4\sigma(F)$, S = 0.934) for compound **2a**, and to wR_2 = 0.057 for 3166 reflections (R_1 = 0.043 for 1284 reflections with $F > 4\sigma(F)$, S = 0.934) for **2a** hydrochloride. The atomic coordinates, geometric parameters of the molecules, and crytallographic data are deposited in the Cambridge Crystallographic Data Center as CCDC 784407 (**2a**) and CCDC 791211 (**2a** hydrochloride).

3-Amino-[2-(3,4-dimethoxyphenyl)ethyl]quinazolin-4(3*H*)-one (1) was obtained by the cyclization of methyl 2-[2-(3,4-dimethoxyphenyl)ethylcarboxamido]benzoate with hydrazine hydrate by the procedure of [15, 16].

9,10-Dimethoxy-6,7,12,13-tetrahydro-15*H*-quinazolino[3,2-*c*][2,3]benzodiazocin-15-one Hydrochloride (2a). Paraformaldehyde (1 mmol) and conc. HCl (4 ml) were added to a solution of amine **1** (1 mmol) in dioxane (1-2 ml). The mixture was heated at 80°C for 4 h, cooled, water (5 ml) was added, and the mixture was maintained at -10°C. The precipitate of **2a** hydrochloride was filtered off and washed with acetone. Crystals for X-ray structural analysis were obtained by crystallization from 90% aqueous 2-propanol.

9,10-Dimethoxy-12-(4-pyridyl)-6,7,12,13-tetrahydro-15*H*-quinazolino[3,2-*c*][2,3]benzodiazocin-15-one (2d). 4-Pyridinecarboxaldehyde (1 mmol) and conc. HCl (4 ml) were added to a solution of amine **1** (1 mmol) in dioxane (1-2 ml). The mixture was heated at 80°C for 4 h, cooled, diluted with water, and unreacted starting amine was filtered off. The filtrate was neutralized with 10% aqueous ammonia solution to a weakly alkaline reaction. The mixture was left for 1 h, then the precipitated crystals were filtered off and washed with water. The product was crystallized from a DMF–acetonitrile mixture.

9,10-Dimethoxy-12-R-6,7,12,13-tetrahydro-15*H*-quinazolino[3,2-*c*][2,3]ones 2b,c,e,f (General Method). A mixture of amine **1** (2 mmol) and the corresponding carbonyl compound (2 mmol) in trifluoroacetic acid (5 ml) was boiled for 48 h. The reaction mixture was cooled, diluted with water and neutralized with 10% aqueous ammonia solution to weakly alkaline reaction. The reaction mixture was left for 1 h, then crystals were filtered off, washed with water, and crystallized from a DMF–acetonitrile mixture.

Under these conditions the interaction of amine **1** with 4-formylpyridine leads to 2-[2-(3,4-dimethoxyphenyl)ethyl]-3-[(*E*)-1-(4-pyridyl)methylideneamino]quinazolin-4(3*H*)-one **3.**

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