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Reaction of 1-substituted 3-(2-hydroxyethylamino)quinoline-2,4(1*H*,3*H*)-diones with isothiocyanic acid

Antonín Klásek[1]*, Antonín Lyčka[2], Michal Rouchal[1], Radek Bartošík[1]

[1] *Department of Chemistry, Faculty of Technology, Tomas Bata University, CZ-76272 Zlín, Czech Republic; e-mail: klasek@utb.cz*

[2] *Research Institute for Organic Syntheses (VUOS), CZ-533 54 Pardubice, Czech Republic; e-mail: Antonin.Lycka@vuos.com*

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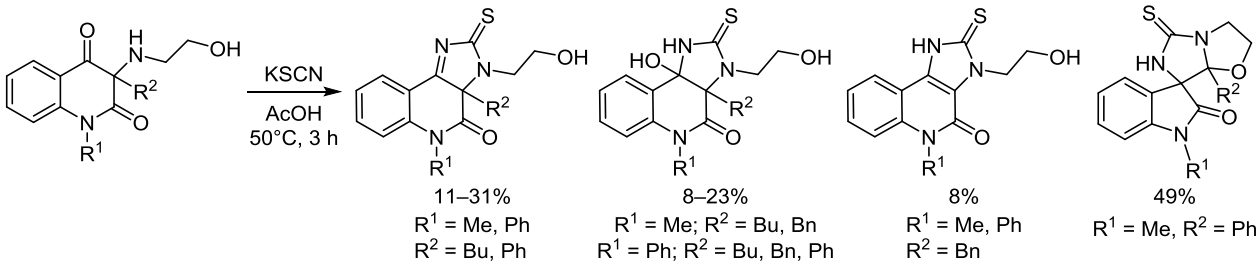


3-Chloroquinoline-2,4-diones react with ethanolamine in the form of 3-(3-hydroxyethylamino)quinoline-2,4-diones. These compounds afford, depending on substituents in positions 1 and 3, four different products from their reaction with isothiocyanic acid: 3-(2-hydroxyethyl)-2-thioxo-3,3a-dihydro-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones, 9b-hydroxy-3-(2-hydroxyethyl)-2-thioxo-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4(2*H*)-ones, 3-(2-hydroxyethyl)-2-thioxo-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones, or 1'-methyl-7a-phenyl-5-thioxo-3,5,6,7a-tetrahydro-2*H*-spiro[imidazo[5,1-*b*]oxazole-7,3'-indolin]-2'-one.

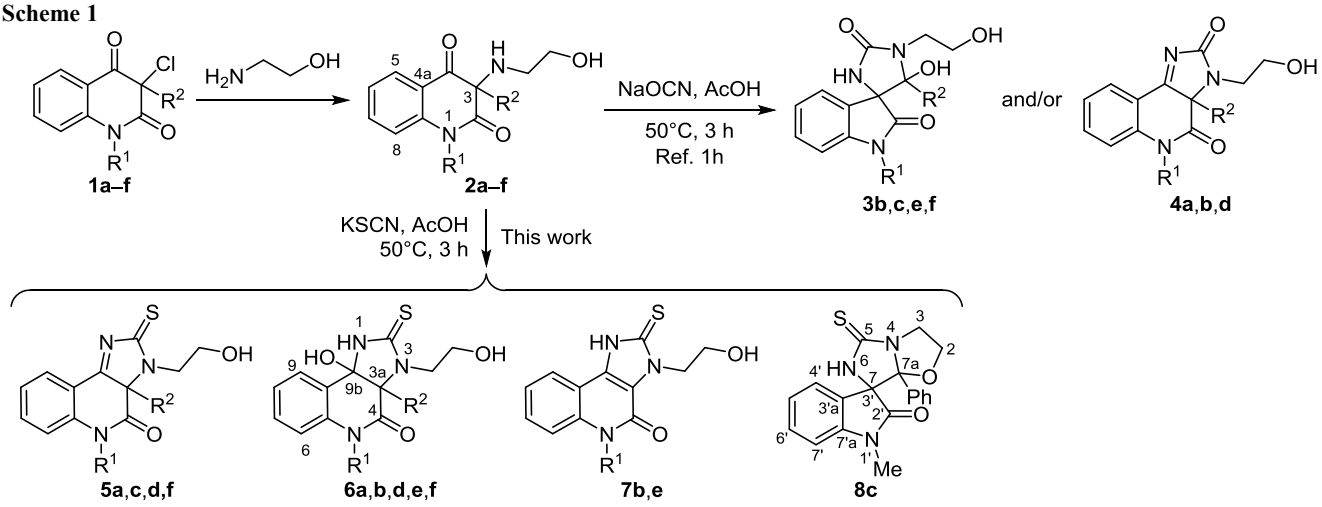
Keywords: isocyanic acid, isothiocyanic acid, 2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(2*H*)-ones, 2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones, quinoline-2,4-diones, nuclear magnetic resonance, rearrangement.

The chemistry of quinolinediones, and in particular, 3-aminoquinoline-2,4-diones have been of interest to our group for a long time.[1] In the literature, two derivatives of 3-aminoquinoline-2,4-diones are mentioned in connection with their biological activity. 3-Amino-3-(4-fluorophenyl)-1*H*-quinoline-2,4-dione is effective against oxidative stress-related diseases[2] and inhibits cisplatin-induced hearing loss through suppression of reactive oxygen species.[3,4] A similar effect is exhibited by 3-amino-6-fluoro-3-(4-fluorophenyl)-1*H*-quinoline-2,4-dione.[4] Therefore, we tried to prepare some 3-aminoquinoline-2,4-dione derivatives with the 3-amino group fixed in a fused ring structure. 3-Aminoquinoline-2,4(1*H*,3*H*)-diones were prepared in our laboratory from 3-chloroquinoline-2,4-diones and ammonia or primary amines.[1a] We found, that these compounds undergo molecular rearrangements when reacting with isocyanic acid that is formed from urea in boiling acetic acid. Through this synthetic route, 2,6-dihydroimidazo[1,5-*c*]-quinolone-2,4-diones and rearranged 3,3a-dihydro-5*H*-imidazo[4,5-*c*]quinazoline-3,5-diones, 3-(3-acylureido)-2,3-dihydro-1*H*-indol-2-ones, and 4-alkylidene-1'*H*-spiro-[imidazolidine-5,3'-indole]-2,2'-diones were prepared.[1b,c] Later we found that the preferable source of isocyanic acid is sodium cyanate and that an acceptable source of isothiocyanic acid is potassium thiocyanate, both in acetic acid solution. Under these conditions, we prepared new heterocycles, e. g., spiro-linked imidazoline-2-thiones and thioxo derivatives of imidazo[1,5-*c*]quinazolin-5-ones and imidazo[4,5-*c*]quinolin-4-ones.[1g]

In an effort to discover an influence of other substituents in the molecule of the amine, we chose ethanolamine as an easily accessible and inexpensive reagent. In our last paper,[1h] we described its reaction with 3-chloroquinoline-2,4-diones **1**. According to expectations, 3-(2-hydroxyethylamino)quinoline-2,4-diones **2** were obtained and their reaction with isocyanic acid afforded mainly 5-hydroxy-1-(2-hydroxyethyl)-1*H*-spiro[imidazolidine-4,3'-indole]-2,2'-diones **3**, but also 3-(2-hydroxyethyl)-3,3a-dihydro-2*H*-imidazo[4,5-*c*]quinoline-2,4-(5*H*)-diones **4** (Scheme 1).

In this paper, the analogous reaction of compounds **2** with isothiocyanic acid is described. The starting compounds **2a**–**f** were reacted with isothiocyanic acid generated *in situ* from potassium thiocyanate in acetic acid. The composition of products from this reaction was

Scheme 1



a R^1 = Me, R^2 = Bu; **b** R^1 = Me, R^2 = Bn; **c** R^1 = Me, R^2 = Ph; **d** R^1 = Ph, R^2 = Bu; **e** R^1 = Ph, R^2 = Bn; **f** R^1 = R^2 = Ph

different from that with isocyanic acid and comprised three different *N*-hydroxyethyl substituted 2-thioxo-1*H*-imidazo-[4,5-*c*]quinolin-4-ones **5a**,**c**,**d**,**f**, **6a**,**b**,**d**,**e**,**f**, and **7b**,**e**, and, in one case, a product of molecular rearrangement **8c** with spiro[imidazo[5,1-*b*]oxazole-7,3'-indolin]-2'-one structure (Scheme 1, Table 1). It is noteworthy that the respective non-cyclized thioureas derived of compounds **2** were never isolated.

It can be expected, that compounds **3** and **5** can probably arise from hydroxyethyl derivative **2** by known Marckwald synthesis.[5] However, no strong acid is present in the reaction mixture. Therefore, we offer another interpretation, based on the formation of isocyanic or isothiocyanic acids during the reaction. With moderately strong isocyanic acid (pK_a 3.7),[6] arising from the isomerization of weak cyanic acid (pK_a 5.4),[7] compounds **2a**,**b**,**d**–**f** react to form[1h] compounds **3a**,**b** and **4d**–**f**. However, isothiocyanic acid is a very strong acid (pK_a –1.3)[7,8] and arises from the isomerization of weak thiocyanic acid (pK_a 5.4).[7] Its reaction with 3-aminoquinoline-2,4(1*H*,3*H*)-diones **2** afforded not only compounds **5a**,**c**,**d**,**f** which are thio analogs of products **4**, obtained by the reaction with isocyanic acid, but also new structures containing sulfur atom, such as dealkylated products **7b**,**e**, due to the influence of strong isothiocyanic acid.

The explanation of the origin of the obtained compounds was based on the NMR spectroscopy. Yellow or orange compounds **5a**,**c**,**d**,**f** were produced in moderate yield from compounds **2a**,**c**,**d**,**f** through the reaction with HNCS. The signals of NCH_2 protons resonate more downfield than the signals of OCH_2 protons. It was surprising, however, the location was proved by 2D NMR (mainly HSQC and HSQC–TOCSY). Protons are situated on the periphery of a molecule and their resonance can be relatively easily influenced by different neighbouring groups.

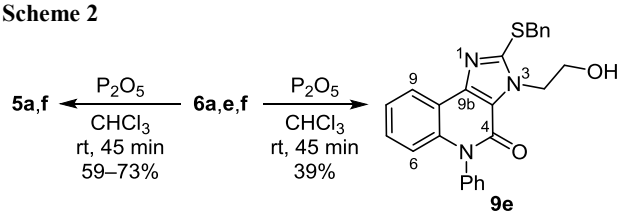
When compound **5a** was kept for one month in DMSO-d_6 the NMR spectrum indicated conversion into compound **6a,** the product of a nucleophilic attack on compound **5a** by H_2O, with a yield of about 65%. Typical ^{13}C chemical shifts in the spectra of this condensation product agree with those in oxa-analog of compound **6a**, except that it has a different alkyl substituent at N-3 atom.[1i] On the other hand, compounds **6** can also be an antecedent of compounds **5**.[1g] Indeed, yellow compounds **5a**,**f** were prepared in high yields through the dehydration of colorless **6a**,**f** upon treatment with P_2O_5 (Scheme 2). However, the same treatment of compound **6e** does not result in compound **5e**, instead, colorless compound **9e** was isolated with 39% yield (Scheme 2). It is likely that this new compound must originate from *C*-debenzylation and subsequent *S*-benzylation with benzyl cation.

Table 1. Products of the reactions of compounds **2a**–**f** with HNCS

Starting material	R^1	R^2	Product (yield, %)
2a	Me	Bu	**5a** (24), **6a** (16), **2a*** (26), *N*-methylisatin (7)
2b	Me	Bn	**6b** (8), **7b** (8)
2c	Me	Ph	**5c** (11), **8c** (49)
2d	Ph	Bu	**5d** (30), **6d** (9), **2d*** (33), *N*-phenylisatin (3)
2e	Ph	Bn	**6e** (27), **7e** (8)
2f	Ph	Ph	**5f** (31), **6f** (23), *N*-phenylisatin (6)

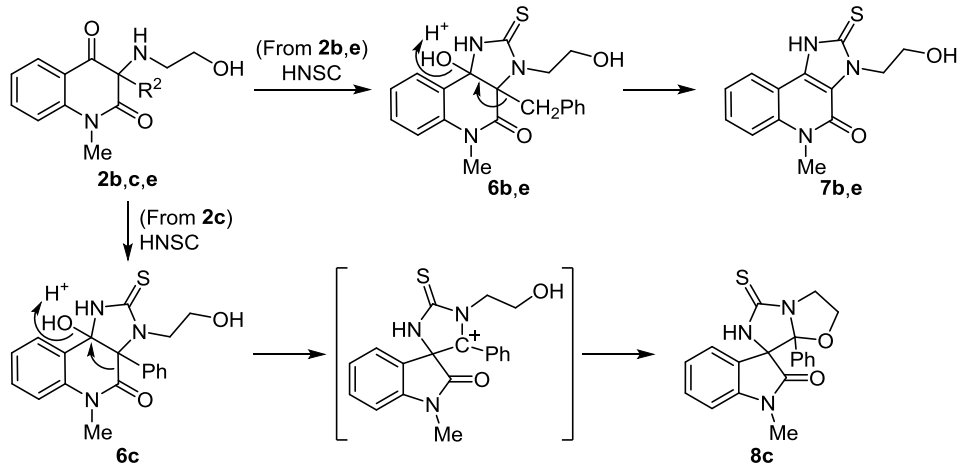
* Recovered starting material.

Scheme 2



In the first-order positive-ion ESI-MS spectra of compounds **5a**,**c**,**d**,**f**, we observed three singly charged signals, which we assigned to $[M+H]^+$, $[M+Na]^+$, and $[M+K]^+$. In the first-order negative-ion ESI-MS spectra of compounds **6**, singly charged signals assigned to $[M–H]^-$, $[M+Cl]^-$, and $[2M–H]^-$ were detected. Moreover, singly charged ion with *m*/*z* 150 in the mass spectra of compounds **6a**,**b** and *m*/*z* 212 in the mass spectra of compounds **6d**,**e**,**f** were observed in the negative ionization mode. We

Scheme 3



assigned these ions to 1-[2-(methylamino)phenyl]ethanolate and 1-[2-(phehylamino)phenyl]ethanolate, respectively. We propose that these ions are products of in-source fragmentation of deprotonated molecular ion $[M–H]^-$.

The only product of molecular rearrangement is compound **8c**, having two aliphatic quaternary carbons, unlike its isomer **5c**. In agreement with our preceding results, this compound must originate from the molecular rearrangement of compound **6c** (Scheme 3). In three cases (Table 1), the corresponding isatins were isolated in addition to the main product, which is indicative of the extensive degradation of the starting compound **2** by isothiocyanic acid. Compounds **7b**,**e** (Scheme 3) arise from the debenzylation of starting compounds **2b**,**e**, bearing a benzyl group at position 3. Such reaction, resulting from the presence of strongly acidic isothiocyanic acid, has been observed before.[1a]

In conclusion, we would like to emphasize that our results provide new information about the behavior of reactive quinoline-2,4-dione systems. 3-(2-Hydroxyethylamino)quinolinediones, prepared from 3-chloroquinoline-dione and ethanolamine, react with isothiocyanic acid to form four different heterocyclic structures: three related imidazo[4,5-*c*]quinolin-4-ones and spiro[imidazo[5,1-*b*]-oxazole-7,3'-indolin]-2'-one, a new tetracyclic spiro system that has not been previously described. Unfortunately, the latter compound arises in only one case and our experiments on the preparation of other similar spiro compounds were so far unsuccessful. This study also demonstrated a new example of benzyl group migration from carbon to sulfur atom. An important result is also dehydration of 9b-hydroxy-2-thioxo-4*H*-imidazo[4,5-*c*]-quinolin-4-ones to 2-thioxo-4*H*-imidazo[4,5-*c*]quinolin-4-ones enabling preparation of these compounds as the only product by the two-step reaction from starting 3-aminoquinoline-2,4-diones. The prepared compounds are suitable for biological testing as well as further synthetic elaboration.

Experimental

IR spectra were recorded on a Smart OMNI-Transmission Nicolet iS10 spectrophotometer in KBr pellets. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker Avance III HD 500 spectrometer (500, 125, and 50 MHz, respectively) in DMSO-d_6; the ^{1}H and ^{13}C chemical shifts are given with respect to internal standard TMS; for ^{15}N spectra, $MeNO_2$ was used as an external standard in a co-axial capillary; signal assignments were carried out using APT and 2D experiments (gradient-selected (gs) ^{1}H–^{1}H COSY, gs-^{1}H–^{1}H TOCSY, gs-^{1}H–^{13}C HMQC, gs-^{1}H–^{13}C HMQC-RELAY, gs-^{1}H–^{13}C HMBC, gs-^{1}H–^{15}N HMBC).[9–11] Mass spectra were recorded on a Bruker Daltonics amaZon X ion-trap mass spectrometer, equipped with an ESI source; individual samples were injected into the ESI source as MeOH–H_2O solutions (concentration 500 ng/ml) *via* a syringe pump with a constant flow rate of 3 ml/min; *m*/*z* range 50–1500, electrospray voltage ±4.2 kV, drying gas temperature 220°C, drying gas flow rate 6.0 dm^3/min, nebulizer pressure 55.16 kPa, capillary exit voltage 140 V; N_2 was used as both nebulizing and drying gas. Elemental analysis was carried out on a Thermo Fisher Scientific Flash EA 1112 elemental analyzer. Melting points were determined using a Kofler block. TLC was performed using Macherey-Nagel Alugram® SIL G/UV_{254} foil plates; elution with PhH–AcOEt, 4:1, $CHCl_3$–EtOH, 9:1, or $CHCl_3$–AcOEt, 7:3. Column chromatography was carried out on Merck silica gel (grade 60, 70–230 mesh); elution with $CHCl_3$, then $CHCl_3$–EtOH, 99:1→8:2, or PhH, then PhH–AcOEt, 99:1→8:2.

Compounds **2a–f** were prepared from the respective compounds **1a–f** and ethanolamine.[1a]

Reaction of compounds 2a–f with HNCS (General method). KSCN (0.874 g, 9 mmol) was added to a solution of compound **2a–f** (1.5 mmol) in AcOH (4.5 ml), and the mixture was stirred for 3 h at 50°C. The course of the reaction was monitored by TLC. After cooling, the mixture was poured onto crushed ice (20 ml) and extracted with $CHCl_3$ (5 × 15 ml) and then with AcOEt (5 × 15 ml). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was separated by column chromatography.

3a-Butyl-3-(2-hydroxyethyl)-5-methyl-2-thioxo-2,3,3a,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (5a) was prepared from compound **2a**. Yield 24%. Orange solid. Mp 135–137°C (PhH–cyclohexane). IR spectrum, ν, cm^{-1}: 3376, 2961, 2932, 2875, 1690, 1661, 1609, 1589, 1471, 1439, 1389, 1334, 1287, 1255, 1230, 1211, 1178, 1160, 1110, 1072, 1050, 990, 967, 775, 758, 730, 699, 683, 671,

608, 520. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.68 (3H, t, *J* = 7.3, 4-CH_3 Bu); 0.66–0.76 (2H, m, 2-CH_2 Bu); 1.02–1.13 (2H, m, 3-CH_2 Bu); 1.81–1.90 (1H, m) and 2.33–2.41 (1H, m, 1-CH_2 Bu); 3.32 (3H, s, 5-CH_3); 3.78–3.88 (3H, m, CH_2O, NCH_2); 4.03–4.10 (1H, m, NCH_2); 4.90 (1H, br. s, OH); 7.32–7.37 (1H, m, H-7); 7.43–7.47 (1H, m, H-9); 7.74–7.79 (1H, m, H-8); 7.90–7.94 (1H, m, H-6). ^{13}C NMR spectrum, δ, ppm: 13.6 (C-4 Bu); 21.1 (C-3 Bu); 24.2 (C-2 Bu); 29.9 (5-CH_3); 36.5 (C-1 Bu); 47.2 (NCH_2); 56.8 (CH_2O); 81.2 (C-3a); 116.0 (C-5a); 116.8 (C-9); 124.1 (C-7); 125.8 (C-6); 135.7 (C-8); 141.7 (C-9a); 166.6 (C-4); 183.8 (C-9b); 194.5 (C-2). Mass spectrum, *m*/*z* (I_{rel}, %): 685 $[2M+Na]^+$ (5), 370 $[M+K]^+$ (10), 354 $[M+Na]^+$ (100), 351 $[2M+Ca]^{2+}$ (9), 332 $[M+H]^+$ (12). Found, %: C 61.45; H 6.60; N 12.79; S 9.64. $C_{17}H_{21}N_3O_2S$. Calculated, %: C 61.61; H 6.39; N 12.68; S 9.67.

3-(2-Hydroxyethyl)-5-methyl-3a-phenyl-2-thioxo-2,3,3a,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (5c) was prepared from compound **2c**. Yield 11%. Yellow solid. Mp 170–177°C (PhH–hexane). IR spectrum, ν, cm^{-1}: 3556, 3056, 2937, 2897, 1678, 1608, 1588, 1491, 1468, 1447, 1400, 1361, 1326, 1284, 1222, 1168, 1143, 1123, 1050, 1001, 968, 952, 934, 809, 760, 724, 695, 664, 610, 571, 529. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.17–3.29 (1H, m) and 3.62–3.74 (1H, m, CH_2O); 3.44 (3H, s, 5-CH_3); 3.47–3.59 (1H, m) and 3.68–3.80 (1H, m, NCH_2); 4.73 (1H, t, *J* = 5.7, OH); 6.98–7.02 (2H, m, H-2,6 Ph); 7.23–7.28 (1H, m, H-7); 7.36–7.43 (4H, m, H-9, H-3,4,5 Ph); 7.62–7.66 (1H, m, H-8); 7.82–7.92 (1H, m, H-6). ^{13}C NMR spectrum, δ, ppm: 30.4 (5-CH_3); 47.4 (NCH_2); 56.2 (CH_2O); 83.4 (C-3a); 116.7 (C-5a); 116.8 (C-9); 124.1 (C-7); 125.9 (C-2,6 Ph); 126.1 (C-6); 130.1 (C-3,5 Ph); 130.4 (C-4 Ph); 131.6 (C-1 Ph); 135.5 (C-8); 141.2 (C-9a); 165.0 (C-4); 183.1 (C-9b); 195.0 (C-2). Mass spectrum, *m*/*z* (I_{rel}, %): 725 $[2M+Na]^+$ (9), 390 $[M+K]^+$ (7), 374 $[M+Na]^+$ (100), 371 $[2M+Ca]^{2+}$ (8), 352 $[M+H]^+$ (17). Found, %: C 64.86; H 4.91; N 11.77; S 9.00. $C_{19}H_{17}N_3O_2S$. Calculated, %: C 64.94; H 4.88; N 11.96; S 9.12.

3a-Butyl-3-(2-hydroxyethyl)-5-phenyl-2-thioxo-2,3,3a,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (5d) was prepared from compound **2d**. Yield 30%. Yellow solid. Mp 161–166°C (PhH–hexane). IR spectrum, ν, cm^{-1}: 3454, 3066, 2962, 2929, 2871, 1689, 1608, 1590, 1490, 1467, 1432, 1385, 1340, 1322, 1281, 1245, 1225, 1164, 1108, 1066, 1033, 1004, 962, 859, 777, 754, 733, 696, 633, 610, 582, 516. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78 (3H, t, *J* = 7.3, 4-CH_3 Bu); 0.75–0.85 (2H, m, 2-CH_2 Bu); 1.07–1.23 (2H, m, 3-CH_2 Bu); 2.15–2.27 (1H, m) and 2.48–2.55 (1H, m, 1-CH_2 Bu); 3.73–3.88 (3H, m, CH_2O, NCH_2); 4.05–4.11 (1H, m, NCH_2); 4.83 (1H, t, *J* = 5.3, OH); 6.39–6.44 (1H, m, H-9); 7.27–7.34 (3H, m, H-7, H-2,6 Ph); 7.47–7.64 (4H, m, H-8, H-3,4,5 Ph); 7.96–8.01 (1H, m, H-6). ^{13}C NMR spectrum, δ, ppm: 13.6 (C-4 Bu); 21.1 (C-3 Bu); 24.4 (C-2 Bu); 36.4 (C-1 Bu); 47.2 (NCH_2); 56.8 (CH_2O); 81.5 (C-3a); 115.7 (C-9); 117.3 (C-5a); 124.1 (C-7); 125.9 (C-6); 129.4 (C-2,6 Ph); 129.9 (C-4 Ph); 130.3 (C-3,5 Ph); 130.4 (C-1 Ph); 136.8 (C-8); 142.8 (C-9a); 166.9 (C-4); 183.7 (C-9b); 194.9 (C-2). Mass spectrum, *m*/*z* (I_{rel}, %): 809 $[2M+Na]^+$ (5), 432 $[M+K]^+$ (11), 416 $[M+Na]^+$ (100), 413 $[2M+Ca]^{2+}$ (11), 394 $[M+H]^+$ (15). Found, %: C 67.05; H 6.10; N 10.65; S 8.02. $C_{22}H_{23}N_3O_2S$. Calculated, %: C 67.15; H 5.89; N 10.68; S 8.15.

3-(2-Hydroxyethyl)-3a,5-diphenyl-2-thioxo-2,3,3a,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (5f) was prepared from compound **2f**. Yield 31%. Orange solid. Mp 178–180°C (PhH–cyclohexane). IR spectrum, ν, cm^{-1}: 3451, 3061, 2361, 1702, 1608, 1587, 1492, 1466, 1449, 1394, 1359, 1309, 1289, 1246, 1229, 1165, 1140, 1060, 1037, 1003, 953, 771, 733, 721, 703, 694, 671, 611, 594, 568, 516. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10–3.19 (1H, m) and 3.59–3.66 (1H, m, CH_2O); 3.49–3.58 (1H, m) and 3.79–3.86 (1H, m, NCH_2); 4.68 (1H, t, *J* = 5.7, OH); 6.29–6.34 (1H, m, H-9); 7.17–7.26 (3H, m, H-7, H-2,6 3a-Ph); 7.39–7.69 (9H, m, H-8, H 5-Ph, H-3,4,5 3a-Ph); 7.97–8.02 (1H, m, H-6). ^{13}C NMR spectrum, δ, ppm: 47.3 (NCH_2); 56.1 (CH_2O); 83.6 (C-3a); 116.6 (C-5a); 117.4 (C-9); 124.4 (C-7); 126.1 (C-2,6 3a-Ph); 126.3 (C-6); 128.9 (C-2,6 5-Ph); 130.1 (C-4 5-Ph); 130.3 (C-3,5 3a,5-Ph); 130.5 (C-4 3a-Ph); 131.5 (C-1 5-Ph); 135.1 (C-8); 136.8 (C-1 3a-Ph); 142.3 (C-9a); 165.2 (C-4); 182.9 (C-9b); 195.0 (C-2). Mass spectrum, *m*/*z* (I_{rel}, %): 849 $[2M+Na]^+$ (8), 452 $[M+K]^+$ (8), 436 $[M+Na]^+$ (100), 433 $[2M+Ca]^{2+}$ (21), 414 $[M+H]^+$ (16). Found, %: C 69.81; H 4.75; N 10.18; S 7.74. $C_{24}H_{19}N_3O_2S$. Calculated, %: C 69.71; H 4.63; N 10.16; S 7.75.

3a-Butyl-9b-hydroxy-3-(2-hydroxyethyl)-5-methyl-2-thioxo-1,2,3,3a,5,9b-hexahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (6a) was prepared from compound **2a**. Yield 16%. Colorless solid. Mp 203–217°C (AcOEt). IR spectrum, ν, cm^{-1}: 3418, 3226, 2958, 2933, 2871, 1662, 1605, 1478, 1436, 1365, 1303, 1255, 1205, 1170, 1122, 1054, 1005, 989, 956, 939, 910, 865, 843, 757, 721, 691, 623, 590, 518, 490. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.68 (3H, t, *J* = 7.3, 4-CH_3 Bu); 0.70–0.76 (1H, m) and 0.92–1.01 (1H, m, 2-CH_2 Bu); 1.07–1.15 (2H, m, 3-CH_2 Bu); 1.95 (2H, m, 1-CH_2 Bu); 3.29 (3H, s, 5-CH_3); 3.57–3.65 (2H, m, CH_2O); 3.83–3.90 (2H, m, NCH_2); 4.60 (1H, t, *J* = 6.4, OH); 6.87 (1H, s, 9b-OH); 7.12–7.20 (2H, m, H-6,8); 7.38–7.43 (1H, m, H-7); 7.72–7.79 (1H, m, H-9); 9.14 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.5 (C-4 Bu); 22.5 (C-3 Bu); 24.1 (C-2 Bu); 29.4 (5-CH_3); 31.3 (C-1 Bu); 46.4 (NCH_2); 59.0 (CH_2O); 72.3 (C-3a); 84.7 (C-9b); 114.5 (C-6); 123.3 (C-8); 123.7 (C-9a); 126.3 (C-9); 130.0 (C-7); 136.2 (C-5a); 168.6 (C-4); 181.3 (C-2). ^{15}N NMR spectrum, δ, ppm (*J*, Hz): –237.9 (d, ^1J = 95.6, 1-NH); –252.6 (N-5); –253.3 (N-3). Mass spectrum, *m*/*z* (I_{rel}, %): 721.2 $[2M+Na]^+$ (5), 388 $[M+K]^+$ (11), 372 $[M+Na]^+$ (100), 369 $[2M+Ca]^{2+}$ (26), 350 $[M+H]^+$ (6). Mass spectrum, *m*/*z* (I_{rel}, %): 697 $[2M-H]^-$ (66), 384 $[M+^{35}Cl]^-$ (23), 348 $[M-H]^-$ (100), 150 (86). Found, %: C 58.36; H 6.74; N 11.86; S 8.98. $C_{17}H_{23}N_3O_3S$. Calculated, %: C 58.43; H 6.63; N 12.02; S 9.18.

3a-Benzyl-9b-hydroxy-3-(2-hydroxyethyl)-5-methyl-2-thioxo-1,2,3,3a,5,9b-hexahydro-4*H*-imidazo[4,5-*c*]-quinolin-4-one (6b) was prepared from compound **2b**. Yield 8%. Colorless solid. Mp 205–215°C (PhH–cyclohexane). IR spectrum, ν, cm^{-1}: 3244, 2937, 2887, 1662, 1606, 1477, 1410, 1369, 1304, 1249, 1197, 1132, 1075, 1034, 1016, 961, 944, 896, 832, 790, 756, 740, 701, 621, 596, 550, 526, 456. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (1H, d, *J* = 16.0) and 3.36 (1H, d, *J* = 16.0, C<u>H</u>$_2$Ph);

3.35 (3H, s, 5-CH_3); 3.65–3.81 (2H, s, CH_2O); 4.04–4.08 (2H, m, NCH_2); 4.65 (1H, t, J = 6.3, OH); 6.54–6.56 (1H, m, H-6); 6.81–6.93 (5H, m, H Ph); 6.97–7.02 (1H, m, H-8); 7.07–7.12 (1H, m, H-7); 7.15 (1H, s, 9b-OH); 7.64–7.67 (1H, m, H-9); 9.19 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 29.0 (5-CH_3); 36.2 ($\underline{C}H_2$Ph); 46.9 (NCH_2); 59.2 (CH_2O); 72.9 (C-3a); 84.7 (C-9b); 113.6 (C-6); 122.6 (C-8); 123.0 (C-9a); 126.1 (C-9); 126.7 (C-4 Ph); 126.8 (C-3,5 Ph); 129.2 (C-7); 130.0 (C-2,6 Ph); 132.2 (C-1 Ph); 135.6 (C-5a); 168.1 (C-4); 181.8 (C-2). ^{15}N NMR spectrum, δ, ppm (J, Hz): –237.9 (d, ^1J = 95.6, 1-NH); –250.3 (N-5); –254.0 (N-3). Mass spectrum, m/z (I_{rel}, %): 789 $[2M+Na]^+$ (10), 422 $[M+K]^+$ (13), 406 $[M+Na]^+$ (100), 403 $[2M+Ca]^{2+}$ (15), 384 $[M+H]^+$ (4). Mass spectrum, m/z (I_{rel}, %): 765 $[2M–H]^–$ (47), 418 $[M+^{35}Cl]^–$ (9), 382 $[M–H]^–$ (100), 150 (57). Found, %: C 62.83; H 5.51; N 10.84; S 8.53. $C_{20}H_{21}N_3O_3S$. Calculated, %: C 62.64; H 5.52; N 10.96; S 8.36.

3a-Butyl-9b-hydroxy-3-(2-hydroxyethyl)-5-phenyl-2-thioxo-1,2,3,3a,5,9b-hexahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (6d) was prepared from compound **2d**. Yield 9%. White solid. Mp 220–226°C (PhH). IR spectrum, ν, cm^{-1}: 3283, 3169, 2958, 2932, 2872, 1654, 1606, 1596, 1464, 1430, 1398, 1356, 1304, 1257, 1207, 1127, 1070, 1051, 1006, 966, 945, 857, 754, 720, 699, 681, 649, 628, 586, 511. ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.78 (3H, t, J = 7.0, 4-CH_3 Bu); 1.12–1.31 (4H, m, 2,3-CH_2 Bu); 1.99–2.12 (2H, m, 1-CH_2 Bu); 3.59–3.67 (2H, m, CH_2O); 3.75–3.81 (1H, m) and 3.86–3.93 (1H, m, NCH_2); 4.60 (1H, t, J = 6.2, OH); 6.14–6.17 (1H, m, H-6); 7.00 (1H, s, 9b-OH); 7.11–7.24 (4H, m, H-7,8, H-2,6 Ph); 7.50–7.54 (1H, m, H-4 Ph); 7.57–7.62 (2H, m, H-3,5 Ph); 7.81–7.84 (1H, m, H-9); 9.28 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.5 (C-4 Bu); 22.5 (C-3 Bu); 24.3 (C-2 Bu); 31.7 (C-1 Bu); 46.6 (NCH_2); 59.0 (CH_2O); 72.5 (C-3a); 85.1 (C-9b); 115.5 (C-6); 123.4 (C-8,9a); 126.8 (C-9); 128.3 (C-2,6 Ph); 128.7 (C-4 Ph); 129.6 (C-7); 130.2 (C-3,5); 137.1 (C-5a); 137.4 (C-1 Ph); 168.9 (C-4); 181.5 (C-2). ^{15}N NMR spectrum, δ, ppm (J, Hz): –231.0 (N-5); –237.7 (d, ^1J = 96.0, 1-NH); –254.6 (N-3). Mass spectrum, m/z (I_{rel}, %): 845 $[2M+Na]^+$ (7), 450 $[M+K]^+$ (20), 434 $[M+Na]^+$ (100), 431 $[2M+Ca]^{2+}$ (12), 412 $[M+H]^+$ (3). Mass spectrum, m/z (I_{rel}, %): 821 $[2M–H]^–$ (21), 446 $[M+^{35}Cl]^–$ (27), 410 $[M–H]^–$ (29), 212 (100). Found, %: C 64.14; H 6.28; N 9.98; S 7.85. $C_{22}H_{25}N_3O_3S$. Calculated, %: C 64.21; H 6.12; N 10.21; S 7.79.

3a-Benzyl-9b-hydroxy-3-(2-hydroxyethyl)-5-phenyl-2-thioxo-1,2,3,3a,5,9b-hexahydro-4*H*-imidazo[4,5-*c*]-quinolin-4-one (6e) was prepared from compound **2e**. Yield 27%. Colorless solid. Mp 243–247°C (AcOEt). IR spectrum, ν, cm^{-1}: 3387, 3192, 2933, 1652, 1598, 1491, 1475, 1432, 1397, 1358, 1303, 1239, 1199, 1134, 1067, 1038, 970, 854, 811, 755, 744, 717, 701, 608, 545, 524. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.28 (1H, d, J = 16.0) and 3.54 (1H, d, J = 16.0, $C\underline{H}_2$Ph); 3.63–3.69 (1H, m) and 3.71–3.77 (1H, m, CH_2O); 3.97–4.06 (2H, m, NCH_2); 4.67 (1H, t, J = 6.3, OH); 5.59–5.64 (1H, m, H-6); 6.70–6.85 (2H, m, H Ph); 6.90–7.15 (7H, m, H-7,8, H Ph); 7.38 (1H, s, 9b-OH); 7.38–7.53 (3H, m, H Ph); 7.75–7.80 (1H, m, H-9); 9.39 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 36.3 ($\underline{C}H_2$Ph); 46.9 (NCH_2); 59.2 (CH_2O); 73.3 (C-3a); 85.1 (C-9b); 115.1 (C-6); 123.0 (C-8); 123.1 (C-9a); 126.5 (C-9); 127.1 (C-4 5-Ph); 127.3 (C-3,5 5-Ph); 128.6 (C-3,5 CH_2Ph); 129.1 (C-4 CH_2Ph); 130.0 (C-7); 130.8 (C-2,6 CH_2Ph); 132.4 (C-1 CH_2Ph); 136.8 (C-5a); 137.1 (C-1 5-Ph); 167.9 (C-4); 181.8 (C-2). Mass spectrum, m/z (I_{rel}, %): 913 $[2M+Na]^+$ (8), 484 $[M+K]^+$ (27), 468 $[M+Na]^+$ (100), 465 $[2M+Ca]^{2+}$ (7), 446 $[M+H]^+$ (10). Mass spectrum, m/z (I_{rel}, %): 889 $[2M–H]^–$ (21), 480 $[M+^{35}Cl]^–$ (43), 444 $[M–H]^–$ (22), 212 (100). Found, %: C 67.36; H 5.28; N 9.24; S 7.27. $C_{25}H_{23}N_3O_3S$. Calculated, %: C 67.40; H 5.20; N 9.43; S 7.20.

9b-Hydroxy-3-(2-hydroxyethyl)-3a,5-diphenyl-2-thioxo-1,2,3,3a,5,9b-hexahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (6f) was prepared from compound **2f**. Yield 23%. Colorless solid. Mp 228–235°C (AcOEt). IR spectrum, ν, cm^{-1}: 3230, 2957, 1685, 1661, 1605, 1594, 1491, 1464, 1431, 1390, 1341, 1307, 1260, 1195, 1140, 1077, 996, 945, 930, 863, 832, 759, 735, 704, 691, 630, 606, 589, 574, 532, 513. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.27–3.40 (1H, m, NCH_2); 3.60–3.74 (2H, m, NCH_2, OCH_2); 3.87–3.99 (2H, m, OCH_2); 4.55 (1H, t, J = 5.7, OH); 6.29–6.33 (1H, m, H-6); 7.00 (1H, s, 9b-OH); 7.07–7.13 (1H, m, H-8); 7.20–7.26 (1H, m, H-7); 7.27–7.50 (7H, m, H-2,6 5-Ph, H-2,3,4,5,6 3a-Ph); 7.53–7.58 (1H, m, H-4 5-Ph); 7.61–7.69 (2H, m, H-9, H-3,5 5-Ph); 9.55 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 48.7 (NCH_2); 58.4 (CH_2O); 79.0 (C-3a); 86.5 (C-9b); 116.2 (C-6); 122.5 (C-9a); 123.5 (C-8); 128.0 (C-9); 128.2 (C-2,6 3a-Ph); 128.8 (C-3,5 3a-Ph, C-2,6 5-Ph); 129.9 (C-7); 130.3 (C-3,5 5-Ph); 131.8 (C-1 3a-Ph); 137.4 (C-5a); 137.6 (C-1 5-Ph); 168.0 (C-4); 184.5 (C-2). Mass spectrum, m/z (I_{rel}, %): 885 $[2M+Na]^+$ (4), 470 $[M+K]^+$ (15), 454 $[M+Na]^+$ (100), 451 $[2M+Ca]^{2+}$ (9), 432 $[M+H]^+$ (5). Mass spectrum, m/z (I_{rel}, %): 861 $[2M–H]^–$ (4), 466 $[M+^{35}Cl]^–$ (20), 430 $[M–H]^–$ (59), 212 (100). Found, %: C 66.64; H 4.93; N 9.53; S 7.68. $C_{24}H_{21}N_3O_3S$. Calculated, %: C 66.80; H 4.91; N 9.74; S 7.43.

3-(2-Hydroxyethyl)-5-methyl-2-thioxo-1,2,3,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (7b) was prepared from compound **2b**. Yield 8%. Yellowish solid. Mp 295–310°C (cyclohexane–AcOEt). IR spectrum, ν, cm^{-1}: 3347, 3074, 2925, 2842, 2730, 1670, 1635, 1587, 1524, 1483, 1427, 1393, 1358, 1327, 1261, 1211, 1164, 1115, 1074, 1063, 1043, 1009, 969, 884, 863, 768, 754, 733, 677, 626, 585, 520. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.66 (3H, s, CH_3); 3.71 (2H, t, J = 6.6, CH_2O); 4.56 (2H, t, J = 6.6, NCH_2); 4.84 (1H, br. s, OH); 7.31–7.36 (1H, m, H-8); 7.52–7.62 (1H, m, H-6,7); 8.05–8.09 (1H, m, H-9); 13.75 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 28.9 (CH_3); 46.3 (NCH_2); 58.4 (CH_2O); 110.0 (C-3a); 115.7 (C-6); 117.7 (C-9a); 122.0 (C-8); 122.5 (C-9); 129.4 (C-7); 131.5 (C-9b); 136.8 (C-5a); 153.2 (C-2); 167.1 (C-4). ^{15}N NMR spectrum, δ, ppm (J, Hz): –220.3 (N-3); –223.1 (d, ^1J = 97.5, 1-NH); –240.0 (N-5). Mass spectrum, m/z (I_{rel}, %): 573 $[2M+Na]^+$ (73), 432.5 $[3M+Ca]^{2+}$ (11), 314 $[M+K]^+$ (9), 298 $[M+Na]^+$ (100), 276 $[M+H]^+$ (21). Mass spectrum, m/z (I_{rel}, %): 571 $[2M–2H+Na]^–$ (12), 274 $[M–H]^–$ (100). Found, %: C 56.48; H 4.66; N 15.01; S 11.84. $C_{13}H_{13}N_3O_2S$. Calculated, %: C 56.71; H 4.76; N 15.26; S 11.65.

3-(2-Hydroxyethyl)-5-phenyl-2-thioxo-1,2,3,5-tetrahydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (7e) was prepared from

compound **2e**. Yield 8%. Colorless solid. Mp 275–290°C (AcOEt). IR spectrum, ν, cm^{-1}: 3426, 3056, 2924, 2740, 1668, 1634, 1591, 1569, 1521, 1480, 1463, 1434, 1394, 1341, 1324, 1267, 1238, 1210, 1164, 1121, 1072, 1029, 989, 860, 786, 753, 732, 699, 683, 608, 563, 515. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (2H, td, *J* = 6.7, *J* = 5.7, CH_2O); 4.56 (2H, t, *J* = 6.7, NCH_2); 4.88 (1H, t, *J* = 5.7, OH); 6.56–6.61 (1H, m, H-6); 7.31–7.45 (4H, m, H-7,8, H-2,6 Ph); 7.55–7.68 (3H, m, H-3,4,5 Ph); 8.16–8.20 (1H, m, H-9); 13.95 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 46.4 (NCH_2); 58.5 (CH_2O); 110.1 (C-3a); 116.5 (C-6); 117.9 (C-9a); 122.1 (C-9); 122.8 (C-8); 129.0 (C-4 Ph); 129.3 (C-7); 129.4 (C-2,6 Ph); 130.1 (C-3,5 Ph); 132.4 (C-9b); 137.2 (C-5a); 138.3 (C-1 Ph); 152.5 (C-2); 167.4 (C-4). ^{15}N NMR spectrum, δ, ppm (*J*, Hz): –219.1 (N-5); –220.3 (N-3); –223.9 (d, ^1J = 96.6, 1-NH). Mass spectrum, *m/z* (I_{rel}, %): 697 $[2M+Na]^+$ (14), 376 $[M+K]^+$ (11), 360 $[M+Na]^+$ (100), 338 $[M+H]^+$ (16). Mass spectrum, *m/z* (I_{rel}, %): 336 $[M–H]^–$ (100). Found, %: C 63.95; H 4.50; N 11.98; S 9.27. $C_{18}H_{15}N_3O_2S$. Calculated, %: C 64.08; H 4.48; N 12.45; S 9.50.

1'-Methyl-7a-phenyl-5-thioxo-2,3,5,6-tetrahydro-7a*H*-spiro[imidazo[5,1-*b*]oxazole-7,3'-indolin]-2'-one (8c) was prepared from compound **2c**. Yield 49%. White solid. Mp 221–224°C (hexane–AcOEt). IR spectrum, ν, cm^{-1}: 3289, 3058, 3033, 2968, 2901, 1710, 1612, 1472, 1356, 1293, 1260, 1233, 1193, 1154, 1127, 1093, 1072, 1052, 1024, 1005, 991, 948, 915, 857, 784, 753, 703, 687, 653, 623, 588, 532. ^{1}H NMR spectrum, δ, ppm: 2.67 (3H, s, CH_3); 3.22–3.30 (1H, m, 2-CH_2); 3.40–3.46 and 3.86–3.93 (2H, m, 3-CH_2); 4.51–4.56 (2H, m, 2-CH_2); 6.94–7.01 (3H, m, H-7', H Ph); 7.14–7.18 (1H, m, H-5'); 7.20–7.32 (3H, m, H Ph); 7.43–7.48 (1H, m, H-6'); 7.53–7.56 (1H, m, H-4'); 9.98 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 25.8 (CH_3); 47.9 (C-3); 62.8 (C-2); 71.7 (C-7); 102.9 (C-7a); 108.6 (C-7'); 121.6 (C-3a'); 122.4 (C-5'); 126.0 (C-2,6); 127.7 (C-3,5); 127.9 (C-4'); 129.0 (C-4 Ph); 130.8 (C-6'); 134.2 (C-1 Ph); 144.2 (C-7'); 172.0 (C-2'); 191.9 (C-5). ^{15}N NMR spectrum, δ, ppm (*J*, Hz): 244.7 (N-4); –246.9 (d, ^1J = 96.6, 6-NH); –252.0 (N-1'). Mass spectrum, *m/z* (I_{rel}, %): 352 $[M+H]^+$ (100). Mass spectrum, *m/z* (I_{rel}, %): 350 $[M–H]^–$ (100). Found, %: C 65.12; H 5.01; N 11.72; S 9.28. $C_{19}H_{17}N_3O_2S$. Calculated, %: C 64.94; H 4.88; N 11.96; S 9.12.

Conversion of compounds 6a,e,f to compounds 5a,f and 9e. P_2O_5 (43 mg, 0.30 mmol) was added portionwise to a stirred solution of compound **6a**,**e**,**f** (0.20 mmol) in $CHCl_3$ (4.0 ml) at room temperature. After 45 min, the yellow solution was filtered through a short column of silica gel. The filtrate was evaporated to dryness, and the residue was crystallized. From compounds **6a**,**f**, compounds **5a,f**, identical in all respect to those prepared from compounds **2a**,**f**, were obtained in 59 and 73% yields, respectively. From compound **6e**, colorless compound **9e** was obtained in 39% yield besides compound **7e** (5%).

2-(Benzylsulfanyl)-3-(2-hydroxyethyl)-5-phenyl-3,5-dihydro-4*H*-imidazo[4,5-*c*]quinolin-4-one (9e). Colorless solid. Mp 182–186°C (hexane–benzene). IR spectrum, ν, cm^{-1}: 3317, 3061, 3031, 2962, 1670, 1575, 1492, 1456, 1430, 1359, 1309, 1247, 1223, 1163, 1128, 1056, 1036, 947, 852, 757, 702, 681, 666, 607, 563, 546. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.64–3.69 (2H, m, CH_2O); 4.32–4.36 (2H, m, NCH_2); 4.64 (2H, s, SCH_2); 4.96 (1H, t, *J* = 6.9, OH); 6.55–6.59 (1H, m, H-6); 7.24–7.37 (7H, m, H-7,8, H-2,3,4,5,6 5-Ph); 7.47–7.51 (2H, m, H-2,6 CH_2Ph); 7.58–7.62 (1H, m, H-4 CH_2Ph); 7.62–7.66 (2H, m, H-3,5 CH_2Ph); 8.23–8.27 (1H, m, H-9). ^{13}C NMR spectrum, δ, ppm: 36.5 (SCH_2); 48.0 (NCH_2); 60.1 (CH_2O); 116.0 (C-9a); 116.3 (C-6); 121.1 (C-3a); 121.8 (C-9); 122.6 (C-8); 127.5 (C-4 5-Ph); 128.2 (C-7); 128.5 (C-2,6 5-Ph); 128.8 (C-4 CH_2Ph); 129.0 (C-2,6 CH_2Ph); 129.6 (C-3,5 5-Ph); 130.0 (C-3,5 CH_2Ph); 137.4 (C-1 CH_2Ph); 137.6 (C-1 5-Ph); 138.4 (C-5a); 143.9 (C-9b); 152.5 (C-2); 154.1 (C-4). ^{15}N NMR spectrum, δ, ppm: –137.2 (N-1); –217.6 (N-3); –220.9 (N-5). Mass spectrum, *m/z* (I_{rel}, %): 877 $[2M+Na]^+$ (5), 466 $[M+K]^+$ (8), 450 $[M+Na]^+$ (63), 428 $[M+H]^+$ (100). Mass spectrum, *m/z* (I_{rel}, %): 426 $[M–H]^–$ (100). Found, %: C 70.46; H 5.09; N 9.56; S 7.47. $C_{25}H_{21}N_3O_2S$. Calculated, %: C 70.24; H 4.95; N 9.83; S 7.50.

Supplementary information file containing ^{1}H, ^{13}C, and ^{1}H–^{15}N HMBC NMR spectra of the synthesized compounds is available at the journal website http://hgs.osi.lv.

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