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Multicomponent Synthesis of 3-(Alkylsulfanyl)-8-aryl(hetaryl)-7-acetyl-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles

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Abstract—Multicomponent condensation of 3-aryl(hetaryl)-2,4-diacetyl-5-hydroxy-5-methylcyclohexanones with 2-cyanoethanethioamide and alkylating agents in the presence of morpholine afforded 3-(alkylsulfanyl)-8-aryl(hetaryl)-7-acetyl-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles, 1-[1-amino-6-aryl(hetaryl)-8-hydroxy-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-7-yl]ethanones, and 3,3′-[ethane-1,2-diylbis(sulfanediyl)]bis[7-acetyl-6-hydroxy-1,6-dimethyl-8-(furan-2-yl)-5,6,7,8-tetrahydroisoquinolin-4-carbonitrile].

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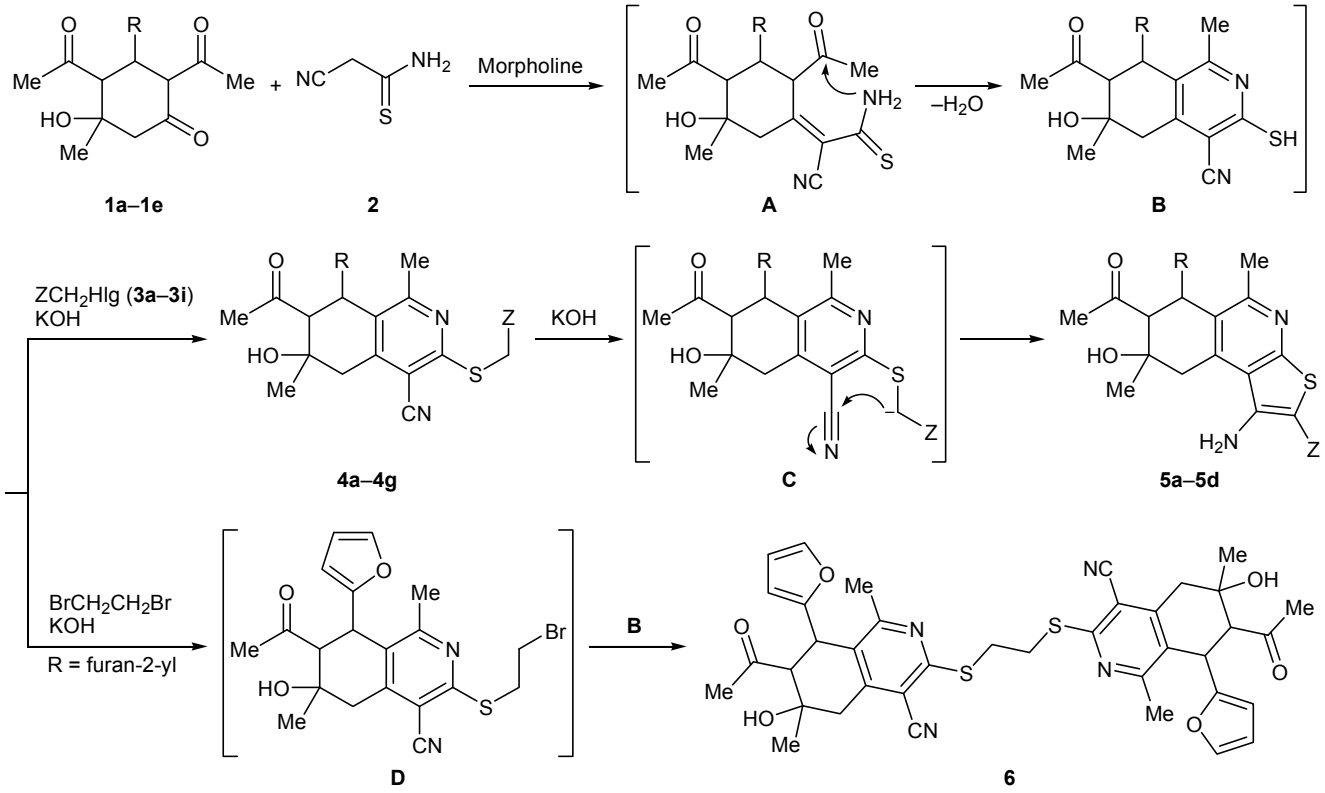
Among methods of synthesis of complex organic compounds, one-pot multicomponent condensations offer a number of advantages such as experimental simplicity, satisfactory yields of target products, short reaction time, and environmental safety [1]. This methodology is especially convenient for the preparation of functionalized nitrogen heterocycles [2–4]. It was applied by us previously to synthesize derivatives of functionally substituted pyridines [5, 6], spiro pyridines [7, 8], partly hydrogenated quinolines [9, 10], and 1,4-dihydro-1,6-naphthyridines [11, 12]. In this work we were the first to synthesize 3-(alkylsulfanyl)-5,6,7,8-tetrahydroisoquinolines by one-pot multicomponent condensation.

The reaction of 3-aryl(hetaryl)-2,4-diacetyl-5-hydroxy-5-methylcyclohexan-1-ones **1a**–**1e** with 2-cyanoethanethioamide (**2**) and alkyl halides **3a**–**3i** in the presence of morpholine at 60°C afforded 3-(alkylsulfanyl)-8-aryl(hetaryl)-7-acetyl-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles **4a**–**4g**. Presumably, the reaction begins with Knoevenagel condensation of cyclohexanone **1** with CH acid **2** to give intermediate alkene **A** which undergoes intramolecular cyclization to 3-sulfanylisoquinoline **B**. Regioselective alkylation of the latter with alkyl halide **3** in basic medium yields compound **4**. When aqueous potassium hydroxide was added to the reaction mixture, the products were partly hydrogenated thieno[2,3-*c*]isoquinolines **5a**–**5d** which were likely to be formed through intermediate **C**. 1,2-Dibromoethane as alkylating agent gave rise to 3,3′-[ethane-1,2-diylbis(sulfanediyl)]bis[7-acetyl-6-hydroxy-1,6-dimethyl-8-(furan-2-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile] (**6**). We failed to isolate intermediate monoalkylation product **D** because of fast further alkylation, regardless of the initial reactant ratio. The best yield of **6** was obtained using 2 equiv of cyclohexanone **1d**, which confirms the proposed scheme (Scheme 1).

The condensation of cyclohexanones **1c** and **1d** with 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**7**) in the presence of sodium ethoxide, other conditions being equal, led to the formation of 9-acetyl-8-hydroxy-8,11-dimethyl-10-phenyl(furan-2-yl)-7,8,9,10-tetrahydrobenzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbonitriles **8a** and **8b** instead of expected 8-alkoxy derivatives. The reaction is likely to involve intermediate **E** (Scheme 2).

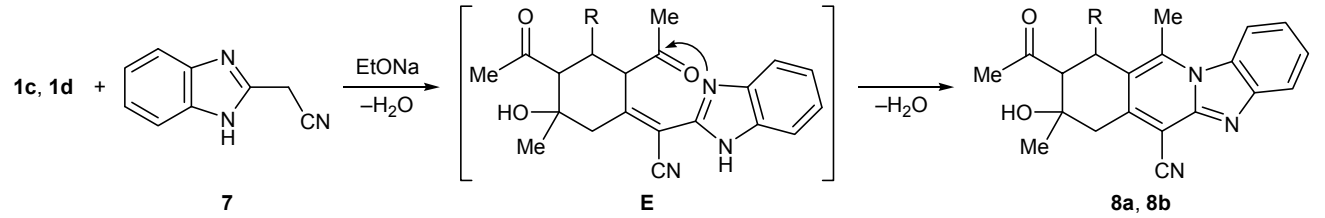
The structure of compounds **4**–**6** and **8** was confirmed by spectral data. Their IR spectra contained absorption bands typical of stretching vibrations of hydroxy, cyano, and carbonyl groups at 3401–3563, 2218–2227, and 1663–1708 cm^{-1}, respectively. Characteristic signals in the ^1H NMR spectra of **4**–**6** and **8** were those belonging to methylene protons in the cyclohexane fragment (C^5H_2, δ 2.80–3.62 ppm, ^2J = 16.5–17.5 Hz) and SCH_2 group (δ 3.77–4.85 ppm, ^2J =

Scheme 1.



1, R = 5-methylfuran-2-yl (**a**), pyridin-3-yl (**b**), Ph (**c**), furan-2-yl (**d**), 4-EtC_6H_4 (**e**); **3**, Hlg = Br, Z = 4-ClC_6H_4CO (**a**), CH_2=CH (**b**), PhCO (**c**); Hlg = Cl, Z = $CONH_2$ (**d**), Ph (**e**), COOMe (**f**), CN (**g**); Hlg = I, Z = H (**h**); **4**, R = Ph, Z = 4-ClC_6H_4CO (**a**), PhNHCO (**b**); R = 4-EtC_6H_4, Z =$CONH_2$ (**c**); R = furan-2-yl, Z = Ph (**d**), CH_2=CH (**e**); R = pyridin-3-yl, Z = PhCO (**f**); R = 5-methylfuran-2-yl, Z = H (**g**); **5**, R = Ph, Z = 4-ClC_6H_4CO (**a**), CN (**b**), R = furan-2-yl, Z = COOMe (**c**); R = 5-methylfuran-2-yl, Z = PhCO (**d**).

Scheme 2.



8, R = Ph (**a**), furan-2-yl (**b**).

13.5–16.7 Hz). In the mass spectra of these compounds we observed a strong peak of the $[CH_3C{\equiv}O]^+$ ion, as well as a low-intense $[M + 2]^+$ ion peak which indicated the presence of a sulfur atom in their molecules [13]. The *m*/*z* values of the molecular ions conformed to the nitrogen rule [14].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum One spectrometer. The ^{1}H NMR spectra were measured on a Bruker Avance instrument at 400.13 MHz from solutions in DMSO-d_6 using tetramethylsilane as internal standard. The mass spectra of **4a**–**4g** and **5a**–**5d** (electron impact, 70 eV) were obtained on an MKh-1321 mass spectrometer with direct sample admission into the ion source, and the mass spectra of **8a** and **8b** were recorded on an Agilent 1100 Series instrument with an Agilent/MSDSL mass-selective detector (electron impact, CF_3COOH matrix). The elemental compositions were determined on a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on

Silufol UV254 plates using acetone–hexane (3:5) as eluent; spots were developed by treatment with iodine vapor or under UV light.

Initial 3-aryl(hetaryl)-2,4-diacetyl-5-hydroxy-5-methylcyclohexan-1-ones **1a**–**1e** were synthesized according to the procedure described in [15].

3-Alkylsulfanyl-8-aryl(hetaryl)-7-acetyl-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles 4a–4g (*general procedure***).** A mixture of 10 mmol of substituted cyclohexanone **1**, 1.0 g (10 mmol) of 2-cyanoethanethioamide (**2**), and 0.87 ml (10 mmol) of morpholine in 20 ml of ethanol was heated under stirring to 60°C and was left to stand for 24 h. To the reaction mixture we added under stirring 5.6 ml (10 mmol) of 10% aqueous potassium hydroxide, 20 ml of DMF, and 10 mmol of alkyl halide **3**, and the mixture was stirred for 1 h and diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane.

7-Acetyl-3-[2-(4-chlorobenzoyl)-2-oxoethylsulfanyl]-6-hydroxy-1,6-dimethyl-8-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4a). Yield 3.4 g (68%), white powder, mp 214–216°C (from EtOH). IR spectrum, ν, cm^{-1}: 3507 (OH), 2219 (C≡N), 1696, 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.24 s (3H, Me), 1.59 s (3H, Me), 2.08 s (3H, Me), 2.82–2.90 m (2H, 5-H, 7-H), 3.25 d (1H, 5-H, ^2J = 17.2 Hz), 4.44 d (1H, 8-H, J = 10.3 Hz), 4.67 d (1H, SCH_2, ^2J = 16.7 Hz), 4.83 d (1H, SCH_2, J = 16.7 Hz), 4.87 br.s (1H, OH), 6.97 d (2H, H_{arom}, J = 7.3 Hz), 7.13–7.24 m (3H, H_{arom}), 7.58 d (2H, H_{arom}, J = 8.4 Hz), 8.03 d (2H, H_{arom}, J = 8.4 Hz). Mass spectrum, m/z (I_{rel}, %): 506 (8) $[M + 2]^+$, 505 (7) $[M]^+$, 504 (23) $[M - H]^+$, 461 (18) $[M - H - CH_3CO]^+$, 443 (43) $[M - H - H_2O - CH_3CO]^+$, 365 (43), 347 (17), 305 (8), 291 (7), 265 (5), 227 (5), 141 (31), 139 (100) $[COC_6H_4Cl]^+$, 111 (24), 43 (65) $[CH_3CO]^+$, 32 (19). Found, %: C 66.43; H 4.80; N 5.41. $C_{28}H_{25}ClN_2O_3S$. Calculated, %: C 66.59; H 4.99; N 5.55. M 505.03.

2-{[7-Acetyl-4-cyano-8-(4-ethylphenyl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-3-yl]sulfanyl}acetamide (4b). Yield 3.0 g (69%), light yellow powder, mp 201–203°C (from BuOH). IR spectrum, ν, cm^{-1}: 3490 (OH), 3407, 3267, 3197 (NH_2), 2221 (C≡N), 1703 (C=O), 1657 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH_2**Me**, J = 7.5 Hz), 1.28 s (3H, Me), 1.98 s (3H, Me), 2.05 s (3H, Me), 2.58 q (2H, C**H**$_2$Me, ^2J = 7.5 Hz), 2.89–2.94 m (2H, 5-H, 7-H), 3.09 d (1H, 5-H, ^2J = 17.1 Hz), 3.77 d and 3.87 d (1H each, SCH_2, ^2J = 15.1 Hz), 4.42 d (1H, 8-H, J = 10.2 Hz), 4.66 br.s (1H, OH), 6.87 d (2H, H_{arom}, J = 7.8 Hz), 6.99 br.s (1H, NH_2), 7.05 d (2H, H_{arom}, J = 7.8 Hz), 7.37 br.s (1H, NH_2). Mass spectrum, m/z (I_{rel}, %): 438 (7) $[M + 1]^+$, 437 (31) $[M]^+$, 395 (22) $[M + H - CH_3C=O]^+$, 394 (100) $[M - CH_3CO]^+$, 379 (24) $[M - CH_2CONH_2]^+$, 377 (31) $[M - H_2O - CH_3C=OH]^+$, 376 (35) $[M - H_2O - CH_3CO]^+$, 359 (72), 331 (63), 319 (48), 227 (10), 115 (4), 43 (80) $[CH_3CO]^+$. Found, %: C 65.70; H 6.01; N 9.48. $C_{24}H_{27}N_3O_3S$. Calculated, %: C 65.88; H 6.22; N 9.60. M 437.55.

7-Acetyl-3-(benzylsulfanyl)-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4c). Yield 3.2 g (75%), light brown powder, mp 115–117°C (from PrOH). IR spectrum, ν, cm^{-1}: 3509 (OH), 2218 (CN), 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.24 s (3H, Me), 2.18 s (6H, Me), 2.80 d (1H, 5-H, ^2J = 17.3 Hz), 2.97–3.14 m (2H, 5-H, 7-H), 4.41 d and 4.54 d (1H each, SCH_2, ^2J = 13.5 Hz), 4.69 d (1H, 8-H, J = 8.9 Hz), 4.95 br.s (1H, OH), 6.08 d (1H, 3′-H, J = 2.6 Hz), 6.35 br.s (1H, 4′-H), 7.18–7.35 m (3H, H_{arom}), 7.41 d (2H, H_{arom}, J = 6.5 Hz), 7.50 d (1H, 5′-H, J = 1.2 Hz). Mass spectrum, m/z (I_{rel}, %): 434 (2) $[M + 2]^+$, 433 (5) $[M + 1]^+$, 432 (17) $[M]^+$, 414 (3) $[M - H_2O]^+$, 389 (7), 281 (3), 371 (21) $[M - H_2O - CH_3CO]^+$, 92 (7) $[PhMe]^+$, 91 (100) $[PhCH_2]^+$, 83 (7), 65 (17), 43 (60) $[CH_3CO]^+$, 31 (5). Found, %: C 69.28; H 5.44; N 6.33. $C_{25}H_{24}N_2O_3S$. Calculated, %: C 69.42; H 5.59; N 6.48. M 432.53.

3-(Allylsulfanyl)-7-acetyl-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4d). Yield 3.1 g (82%), yellow powder, mp 115–116°C (from EtOH). IR spectrum, ν, cm^{-1}: 3473 (OH), 2220 (C≡N), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, Me), 2.14 s (3H, Me), 2.18 s (3H, Me), 2.88–3.18 m (2H, 5-H, 7-H), 3.13 d (1H, 5-H, ^2J = 17.2 Hz), 3.84–3.95 m (2H, SCH_2), 4.69 d (1H, 8-H, J = 9.0 Hz), 4.95 br.s (1H, OH), 5.08 d (1H, =CH_2, J_{cis} = 10.8 Hz), 5.28 d (1H, =CH_2, J_{trans} = 17.6 Hz), 5.77–5.98 m (1H, CH=), 6.08 d (1H, 3′-H, J = 3.1 Hz), 6.34 d.d (1H, 4′-H, J = 2.4 Hz), 7.49 d (1H, 5′-H, J = 1.3 Hz). Mass spectrum, m/z (I_{rel}, %): 382 (5) $[M]^+$, 339 (18) $[M - CH_3CO]^+$, 322 (10) $[M - H_2 - CH_3COH]^+$, 321 (54) $[M - H_2O - CH_3CO]^+$, 281 (5), 239 (4), 43 (100) $[CH_3CO]^+$, 41 (17) $[C_3H_7]^+$, 39 (10). Found, %: C 65.83; H 5.65; N 7.16. $C_{21}H_{22}N_2O_3S$. Calculated, %: C 65.95; H 5.80; N 7.32. M 382.48.

2-[(7-Acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-phenyl-5,6,7,8-tetrahydroisoquinolin-3-yl)sulfanyl]-*N*-phenylacetamide (4e). Yield 3.7 g (76%), yellow needles, mp 198–200°C (from EtOH). IR spectrum, ν, cm^{-1}: 3475 (OH), 3422 (NH), 2222 (CN), 1700 (C=O),

1662 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, Me), 1.89 s (3H, Me), 2.09 s (3H, Me), 2.80–3.00 m (2H, 5-H, 7-H), 3.95–4.31 m (3H, 5-H, SCH_2), 4.50 d (1H, 8-H, J = 10.4 Hz), 4.89 br.s (1H, OH), 6.81–7.89 m (10H, Ph), 10.30 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 487 (2) $[M + 2]^+$, 486 (6) $[M + 1]^+$, 485 (15) $[M]^+$, 467 (2) $[M - H_2O]^+$, 393 (100) $[M - PhNH]^+$, 376 (73), 366 (29), 351 (14), 349 (18), 333 (12), 331 (15), 323 (32), 305 (20), 277 (14), 93 (17) $[PhNH_2]^+$, 43 (63) $[CH_3CO]^+$. Found, %: C 69.06; H 5.47; N 8.53. $C_{28}H_{27}N_3O_3S$. Calculated, %: C 69.25; H 5.60; N 8.65. M 485.6.

7-Acetyl-6-hydroxy-1,6-dimethyl-3-(2-oxo-2-phenylethylsulfanyl)-8-(pyridin-3-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4f). Yield 3.6 g (76%), light yellow powder, mp 215–218°C (from BuOH). IR spectrum, ν, cm^{-1}: 3421 (OH), 2220 (CN), 1708, 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.26 s (3H, Me), 1.61 s (3H, Me), 2.13 s (3H, Me), 2.84–2.93 m (2H, 5-H, 7-H), 3.26 d (1H, 5-H, ^2J = 17.1 Hz), 4.53 d (1H, 8-H, J = 9.8 Hz), 4.70 d and 4.85 d (1H each, SCH_2, ^2J = 16.7 Hz), 4.94 br.s (1H, OH), 7.24 t (1H, H_{arom}, J = 5.7 Hz), 7.39 d (1H, H_{arom}, J = 7.7 Hz), 7.47–7.54 m (2H, H_{arom}), 7.59–7.65 m (1H, H_{arom}), 8.00 d (2H, H_{arom}, J = 7.0 Hz), 8.27 s (1H, H_{arom}), 8.37 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 472 (2) $[M + 1]^+$, 471 (7) $[M]^+$, 453 (3) $[M - H_2O]^+$, 410 (7) $[M - H_2O - CH_3CO]^+$, 105 (100) $[PhCO]^+$, 77 (37) $[Ph]^+$, 43 (15) $[CH_3CO]^+$. Found, %: C 68.59; H 5.20; N 8.76. $C_{27}H_{25}N_3O_3S$. Calculated, %: C 68.77; H 5.34; N 8.91. M 471.57.

7-Acetyl-6-hydroxy-1,6-dimethyl-3-(methylsulfanyl)-8-(5-methylfuran-2-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4g). Yield 2.5 g (67%), white powder, mp 140–141°C (from EtOH). IR spectrum, ν, cm^{-1}: 3516 (OH), 2226 (CN), 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, Me), 2.13 s (3H, Me), 2.18 s (3H, Me), 2.19 s (3H, Me), 2.55 s (3H, Me), 2.80 d (1H, 5-H, ^2J = 17.4 Hz), 3.01 d (1H, 7-H, J = 9.1 Hz), 3.11 d (1H, 5-H, ^2J = 17.4 Hz), 4.60 d (1H, 8-H, J = 9.1 Hz), 4.94 br.s (1H, OH), 5.92 br.s (2H, 3′-H, 4′-H). Mass spectrum, m/z (I_{rel}, %): no $[M]^+$, 352 (3) $[M - H_2O]^+$, 310 (19) $[M - H_2O - CH_3COH]^+$, 309 (80) $[M - H_2O - CH_3CO]^+$, 294 (4), 267 (5), 262 (9), 253 (6), 43 (100) $[CH_3CO]^+$, 31 (9). Found, %: C 64.69; H 5.85; N 7.41. $C_{20}H_{22}N_2O_3S$. Calculated, %: C 64.84; H 5.99; N 7.56. M 370.47.

Substituted thieno[2,3-*c*]isoquinolines 5a–5d were synthesized as described above for compounds **4** with the difference that 5.6 ml (10 mmol) of 10% aqueous potassium hydroxide was added to the reaction mixture instead of dilution with water.

1-{1-Amino-2-(4-chlorobenzoyl)-8-hydroxy-5,8-dimethyl-6-phenyl-6,7,8,9-tetrahydrothieno[2,3-*c*]-isoquinolin-7-yl}ethanone (5a). Yield 3.7 g (74%), yellow powder, mp 160–163°C (from AcOH). IR spectrum, ν, cm^{-1}: 3435 (OH), 3283, 2963, 2922 (NH_2), 1702, 1663 (C=O), 1590 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.32 s (3H, Me), 1.99 s (3H, Me), 2.14 s (3H, Me), 3.62 d (1H, 5-H, ^2J = 17.5 Hz), 4.63 d (1H, 8-H, J = 9.5 Hz), 4.78 br.s (1H, OH), 6.95–7.19 m (2H, H_{arom}), 7.15–7.27 m (3H, H_{arom}), 7.60 d (2H, H_{arom}, J = 8.1 Hz), 7.78 d (2H, H_{arom}, J = 8.1 Hz), 7.94 br.s and 8.22 br.s (1H each, NH_2); the signals from the second 5-H proton and 7-H were overlapped by the signal of water. Mass spectrum, m/z (I_{rel}, %): 507 (5) $[M + 2]^+$, 506 (22) $[M + 1]^+$, 505 (18) $[M]^+$, 504 (50) $[M - 1]^+$, 486 (12) $[M - H - H_2O]^+$, 445 (19) $[M - H_2O - CH_3COH]^+$, 444 (15) $[M - H_2O - CH_3CO]^+$, 443 (46) $[M - H - H_2O - CH_3CO]^+$, 367 (12), 141 (32), 139 (100) $[4\text{-}ClC_6H_4CO]^+$, 111 (18), 43 (33) $[CH_3CO]^+$, 31 (12). Found, %: C 66.41; H 4.83; N 5.38. $C_{28}H_{25}ClN_2O_3S$. Calculated, %: C 66.59; H 4.99; N 5.55. M 505.03.

Methyl 1-amino-7-acetyl-6-(furan-2-yl)-8-hydroxy-5,8-dimethyl-6,7,8,9-tetrahydrothieno[2,3-*c*]-isoquinoline-2-carboxylate (5b). Yield 3.0 g (72%), light yellow crystals fluorescing under UV radiation, mp 257–258°C (from BuOH). IR spectrum, ν, cm^{-1}: 3434 (OH), 3347, 3267, 2962 (NH_2), 1705, 1687 (C=O), 1556 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 1.29 s (3H, Me), 2.14 s (3H, Me), 2.23 s (3H, Me), 2.98 d (1H, 7-H, J = 9.8 Hz), 3.28 d and 3.47 d (1H, 5-H, ^2J = 17.4 Hz), 3.79 s (3H, OMe), 4.77 d (1H, 8-H, J = 9.8 Hz), 4.85 br.s (1H, OH), 6.05 d (1H, 3′-H, J = 3.1 Hz), 6.34 d.d (1H, 4′-H, J = 2.4 Hz), 6.81–6.92 m (2H, 5′-H, NH_2), 7.48 br.s (1H, NH_2). Mass spectrum, m/z (I_{rel}, %): 416 (2) $[M + 2]^+$, 415 (7) $[M + 1]^+$, 414 (25) $[M]^+$, 396 (12) $[M - H_2O]^+$, 353 (9) $[M - H_2O - CH_3CO]^+$, 339 (9), 322 (26), 321 (100), 43 (21) $[CH_3CO]^+$. Found, %: C 60.73; H 5.15; N 6.58. $C_{21}H_{22}N_2O_3S$. Calculated, %: C 60.85; H 5.35; N 6.76. M 414.47.

1-{1-Amino-2-benzoyl-8-hydroxy-5,8-dimethyl-6-(5-methylfuran-2-yl)-6,7,8,9-tetrahydrothieno-[2,3-*c*]isoquinolin-7-yl}ethanone (5c). Yield 3.7 g (79%), yellow powder, mp 225–227°C (from AcOH). IR spectrum, ν, cm^{-1}: 3435 (OH), 3309, 2921, 2855 (NH_2), 1698, 1665 (C=O), 1595 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.32 s (3H, Me), 2.12 s (3H, Me), 2.21 s (3H, Me), 2.22 s (3H, Me), 3.02 d (1H, 7-H, J = 9.4 Hz), 3.25 d and 3.51 d (1H each, 5-H, ^2J = 17.1 Hz), 4.69 d (1H, 8-H, J = 9.4 Hz), 4.78 br.s (1H, OH), 5.87 d (1H, 3′-H, J = 2.9 Hz), 5.91 d (1H, 4′-H,

J = 2.9 Hz), 7.38–7.61 m (3H, Ph), 7.69–7.77 m (2H, Ph), 8.08 br.s (2H, NH_2). Mass spectrum, m/z (I_{rel}, %): 476 (2) $[M + 2]^+$, 475 (9) $[M + 1]^+$, 474 (32) $[M]^+$, 456 (5) $[M - H_2O]^+$, 414 (23) $[M - H_2O - CH_3COH]^+$, 413 (78) $[M - H_2O - CH_3CO]^+$, 105 (100) $[PhCO]^+$, 77 (36) $[Ph]^+$, 43 (37) $[CH_3CO]^+$. Found, %: C 68.18; H 5.37; N 5.71. $C_{27}H_{26}N_2O_4S$. Calculated, %: C 68.33; H 5.52; N 5.90. M 474.57.

1-Amino-7-acetyl-8-hydroxy-5,8-dimethyl-6-phenyl-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carbonitrile (5d). Yield 3.2 g (83%), light yellow powder, mp 285–286°C (from AcOH). IR spectrum, ν, cm^{-1}: 3430 (OH), 3357, 3249, 2921 (NH_2), 2204 (CN), 1702 (C=O), 1645 (δNH). ^1H NMR spectrum, δ, ppm: 1.28 s (3H, Me), 1.98 s (3H, Me), 2.13 s (3H, Me), 2.82 d (1H, 7-H, J = 9.3 Hz), 3.22 d and 3.58 d (1H each, 5-H, ^2J = 17.0 Hz), 4.61 d (1H, 8-H, J = 9.3 Hz), 4.73 br.s (1H, OH), 6.56 br.s (2H, NH_2), 6.96 d (2H, Ph, J = 7.3 Hz), 7.11–7.28 m (3H, Ph). Mass spectrum, m/z (I_{rel}, %): 393 (2) $[M + 2]^+$, 392 (8) $[M + 1]^+$, 391 (28) $[M]^+$, 373 (16) $[M - H_2O]^+$, 331 (10) $[M - H_2O - CH_3COH]^+$, 330 (100) $[M - H_2O - CH_3CO]^+$, 316 (15) $[M - H_2O - CH_3COH - CH_3]^+$, 254 (34), 91 (6), 43 (80) $[CH_3CO]^+$. Found, %: C 67.33; H 5.29; N 10.60. $C_{22}H_{21}N_3O_2S$. Calculated, %: C 67.50; H 5.41; N 10.73. M 391.49.

3,3′-[Ethane-1,2-diylbis(sulfanediyl)]bis[7-acetyl-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile] (6) was synthesized as described above for compounds **4** using 0.45 ml (5 mmol) of 1,2-dibromoethane. Yield 2.3 g (64%), colorless needles fluorescing under UV irradiation, mp 235–237°C (from DMF). IR spectrum, ν, cm^{-1}: 3563 (OH), 2221 (CN), 1702 (C=O). ^1H NMR spectrum, δ, ppm: 1.29 s (6H, Me), 2.14 s (6H, Me), 2.19 s (6H, Me), 2.86 d and 2.97 d (2H each, 5-H, ^2J = 17.1 Hz), 3.06 d (2H, 7-H, J = 8.6 Hz), 3.50–3.62 m (4N, CH_2CH_2), 4.62 d (2H, 8-H, J = 8.6 Hz), 4.84 br.s (2H, OH), 6.00 d (2H, 3′-H, J = 2.5 Hz), 6.30 s (2H, 4′-H), 7.38 s (2H, 5′-H). Mass spectrum, m/z (I_{rel}, %): no $[M]^+$, 646 (2), 369 (5), 368 (14), 367 (65), 366 (12), 350 (15), 349 (100), 348 (18), 323 (17), 322 (41), 307 (30), 281 (38), 280 (55), 265 (13), 240 (14), 214 (6), 44 (55) $[CH_3COH]^+$, 43 (25) $[CH_3CO]^+$, 30 (32) $[CH_2O]^+$. Found, %: C 64.11; H 5.22; N 7.75. $C_{38}H_{38}N_4O_6S_2$. Calculated, %: C 64.21; H 5.39; N 7.88. M 710.87.

9-Acetyl-8-hydroxy-8,11-dimethyl-10-phenyl-7,8,9,10-tetrahydrobenzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbonitrile (8a). A solution of 0.23 g (10 mmol) of sodium in 35 ml of anhydrous ethanol was added to a mixture of 2.9 g (10 mmol) of cyclohexanone **1a** and 1.6 g (10 mmol) of 2-(1*H*-benzimidazol-2-yl)acetonitrile (**7**), and the mixture was heated for 1 h under reflux and left to stand for 24 h. The mixture was cooled, and the precipitate was filtered off and washed with ethanol and hexane. Yield 3.3 g (82%), yellow powder fluorescing under UV irradiation, mp 170–172°C (from DMF). IR spectrum, ν, cm^{-1}: 3401 (OH), 2223 (CN), 1704 (C=O). ^1H NMR spectrum, δ, ppm: 1.05 s (3H, Me), 2.00 s (3H, Me), 2.64 s (3H, Me), 3.25 d (1H, 7-H, ^2J = 16.5 Hz), 3.28 d (1H, 9-H, ^2J = 9.6 Hz), 3.40 d (1H, 7-H, ^2J = 16.5 Hz), 4.74 d (1H, 10-H, J = 9.6 Hz), 5.42 br.s (1H, OH), 7.00 d (2H, H_{arom}, J = 6.4 Hz), 7.13–7.30 m (4H, H_{arom}), 7.50 t (1H, H_{arom}, J = 7.0 Hz), 7.84 d (1H, H_{arom}, J = 7.6 Hz), 8.10 d (1H, H_{arom}, J = 6.4 Hz). Mass spectrum: m/z 410 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 76.10; H 5.48; N 10.08. $C_{26}H_{23}N_3O_2$. Calculated, %: C 76.26; H 5.66; N 10.26. M 409.48.

9-Acetyl-10-(furan-2-yl)-8-hydroxy-8,11-dimethyl-7,8,9,10-tetrahydrobenzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbonitrile (8b) was synthesized in a similar way from cyclohexanone **1d**. Yield 1.4 g (69%), bright yellow powder fluorescing under UV irradiation, mp 243–245°C (from DMF). IR spectrum, ν, cm^{-1}: 3429 (OH), 2227 (C≡N), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 1.47 s (3H, Me), 2.27 s (3H, Me), 3.00 s (3H, Me), 3.18 d (1H, 7-H, ^2J = 16.5 Hz), 3.36 d (1H, 9-H, J = 5.6 Hz), 4.96 br.s (2H, 10-H, OH), 6.00 s (1H, 3′-H), 6.28 s (1H, 4′-H), 7.33 t (1H, H_{arom}, J = 7.4 Hz), 7.40 s (1H, 5′-H), 7.53 t (1H, H_{arom}, J = 7.4 Hz), 7.86 d (1H, H_{arom}, J = 8.0 Hz), 8.28 d (1H, H_{arom}, J = 8.5 Hz); the signal of the second 7-H proton was overlapped by the signal of water. Mass spectrum, m/z (I_{rel}, %): 400 (100) $[M + 1]^+$, 382 (13) $[M + 1 - H_2O]^+$. Found, %: C 71.98; H 5.16; N 10.32. $C_{24}H_{21}N_3O_3S$. Calculated, %: C 72.16; H 5.30; N 10.52. M 399.44.

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