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Synthesis and Transformations of New 3-Oxo(thioxo)-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylic Acid Derivatives

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Abstract—By condensation of 2-benzoyl-1-(morpholin-4-yl)-1-cyanohexene with cyanoacetanilides and monothiomalonodiamide the corresponding 2-substituted 3-oxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles and 3-thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxamide were obtained. The latter was used in the synthesis of 3-alkylthio-1-phenyl-5,6,7,8-hexahydroisoquinoline-4-carboxamides and 3,3-dimethyl-1-oxo-6-phenyl-1,2,7,8,9,10-hexahydro-3*H*-[1,3]thiazino[6,5-*c*]isoquinoline.

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Derivatives of partially hydrogenated isoquinoline-4-carboxylic acids are attractive objects for the biological research. For example, among the amides and nitriles of 3-oxo(thioxo)-2,3,5,6,7,8-hexahydroquinoline-4-carboxylic acid agonists have been found with respect to the cannabinoid type 2 receptor [1, 2], inhibitors of 11-β-hydroxysteroid dehydrogenase [3], as well as the compounds with positive inotropic activity [4]. However, their synthetic potential has not been revealed completely that to some extent hinders the rational search for substances with practically useful properties. In particular, for the series of 3-oxo-2,3,5,6,7,8-hexahydroquinoline-4-carbonitriles only the transformation is known of cyano group to carboxy [1] and amido groups [4]. For their 2-thio analogs examples were describes of modification at the 2 position with a pyranose fragment [5], as well as thieno- and pyridinofusion at the 1–2 positions [6]. For this reason, it seemed expedient to synthesize new representatives of this heterocyclic system and explore the possibility of their further transformations with the participation of functional groups in positions 3 and 4.

Among the methods that have been successfully used for the synthesis of partially hydrogenated functionally 4-substituted isoquinolines [7–12], the method of cyclocondensation of 2-acylcyclohexanones with cyano(thio)acetamide [7] allowing to obtain 1-alkyl-substituted isoquinoline-4-carboxylic acid derivatives is characterized by the high selectivity. In this report we demonstrate the possibility of using the preparatively accessible [13] 2-benzoylcyclohexanone enamine (**I**) in the condensation of this kind.

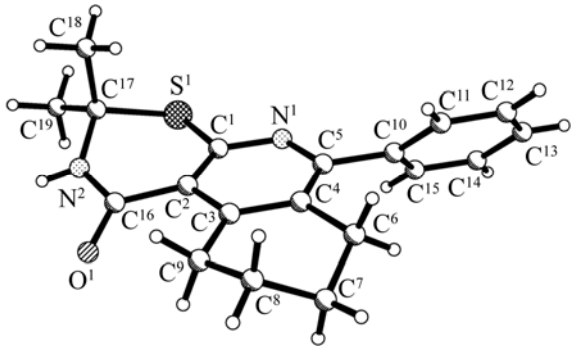
We found that 2-benzoyl-1-(morpholin-4-yl)-1-cyclohexene **I** reacts at room temperature with cyanoacetamides **IIa–IIe** and monothiomalonodiamide **III** in anhydrous ethanol in the presence of equimolar amount of sodium ethoxide to form earlier unknown 2-substituted 3-oxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles **IVa–IVe** and 3-thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxamide **V** in 68–82% and 69% yield respectively. The most probable reaction scheme in the case of the cyanoacetamides **IIa–IIe** seems the reaction by S_NVin mechanism that assumes the formation of intermediates **A** and their subsequent cyclization to the desired products **IVa–IVe.** The ^{13}C NMR spectrum of the latter contain the characteristic signals of the carbon atoms of pyridone ring: C^1 (150–156 ppm), C^3 (158–159 ppm), C^4 (100–101 ppm), C^5 (159–162 ppm), and C^6 (115 ppm). In the case of monothiomalonodiamide **III**, besides the cyclization through the intermediate **B,** the cyclization through the intermediate **C** is not excluded, which would lead to the isomeric 4-thiocarbamoyl-3-oxoisoquinoline **VI**. Spec-

Covalent bond length (*d*) and bond angles (ω) in structure **IX**

Bond	*d*, Å	Bond	*d*, Å	Angle	ω, deg	Angle	ω, deg
S^1–C^1	1.7601(12)	C^4–C^6	1.5167(16)	$C^1S^1C^{17}$	101.00(6)	$C^7C^8C^9$	110.70(11)
S^1–C^{17}	1.8184(13)	C^5–C^{10}	1.4912(16)	$C^1N^1C^5$	117.81(10)	$C^8C^9C^3$	114.67(11)
O^1–C^{16}	1.2328(14)	C^6–C^7	1.5081(18)	$C^{16}N^2C^{17}$	129.60(12)	$C^{15}C^{10}C^{11}$	118.25(12)
N^1–C^1	1.3328(15)	C^7–C^8	1.5051(19)	$N^1C^1C^2$	124.43(11)	$C^{15}C^{10}C^5$	119.43(11)
N^1–C^5	1.3418(14)	C^8–C^9	1.5081(17)	$N^1C^1S^1$	111.65(9)	$C^{11}C^{10}C^5$	122.32(12)
N^2–C^{16}	1.3406(16)	C^{10}–C^{15}	1.3832(17)	$C^2C^1S^1$	123.83(9)	$C^{12}C^{11}C^{10}$	120.61(13)
N^2–C^{17}	1.4512(16)	C^{10}–C^{11}	1.3883(17)	$C^1C^2C^3$	117.52(11)	$C^{13}C^{12}C^{11}$	120.35(14)
C^1–C^2	1.3953(16)	C^{11}–C^{12}	1.3835(19)	$C^1C^2C^{16}$	120.13(10)	$C^{12}C^{13}C^{14}$	119.66(14)
C^2–C^3	1.4200(16)	C^{12}–C^{13}	1.368(2)	$C^3C^2C^{16}$	122.01(10)	$C^{13}C^{14}C^{15}$	120.40(14)
C^2–C^{16}	1.4931(16)	C^{13}–C^{14}	1.3717(19)	$C^4C^3C^2$	118.49(10)	$C^{14}C^{15}C^{10}$	120.72(13)
C^3–C^4	1.4004(16)	C^{14}–C^{15}	1.3809(18)	$C^4C^3C^9$	119.93(10)	$O^1C^{16}N^2$	119.41(11)
C^3–C^9	1.5123(16)	C^{17}–C^{18}	1.5169(19)	$C^2C^3C^9$	121.57(11)	$O^1C^{16}C^2$	121.49(11)
C^4–C^5	1.4061(16)	C^{17}–C^{19}	1.5285(18)	$C^3C^4C^5$	118.49(11)	$N^2C^{16}C^2$	119.00(11)
				$C^3C^4C^6$	121.54(11)	$N^2C^{17}C^{18}$	110.77(11)
				$C^5C^4C^6$	119.87(11)	$N^2C^{17}C^{19}$	108.42(11)
				$N^1C^5C^4$	123.17(11)	$C^{18}C^{17}C^{19}$	111.41(11)
				$N^1C^5C^{10}$	114.03(10)	$N^2C^{17}S^1$	109.15(9)
				$C^4C^5C^{10}$	122.75(11)	$C^{18}C^{17}S^1$	110.41(9)
				$C^7C^6C^4$	113.12(11)	$C^{19}C^{17}S^1$	106.55(10)
				$C^8C^7C^6$	109.30(12)		

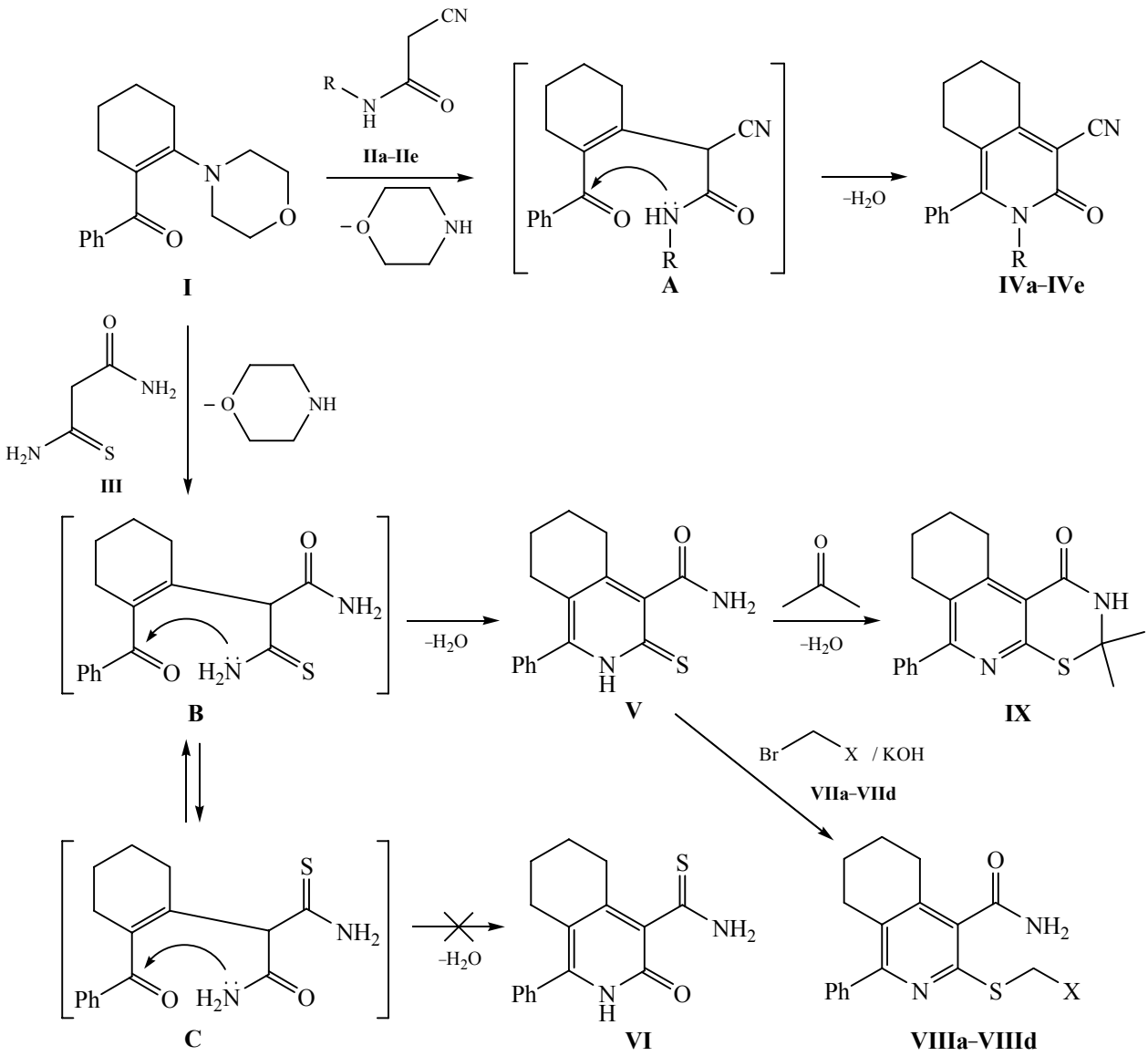
tral characteristics of the compound obtained, in particular, the signals of the carbon atoms in the pyridine ring in ^{13}C NMR spectrum, differ from those of isoquinolines **IV**, but do not allow reliable determination of structure of the compound obtained.

The thiocarbamoyl fragment in the compound **V** is a part of the isoquinoline ring, while in compound **VI** it is exofunctionalized to the ring, therefore its behavior with respect to alkylating agents is expectable to be different. By the example of the reactions with allyl bromide **VIIa**, propargyl bromide **VIIb,** and α-bromoacetophenones **VIIc** and **VIId**, which proceed smoothly in DMF in the presence of KOH, we showed the formation of 3-thiosubstituted isoquinolines **VIIIa–VIIId**. Another important synthetic evidence of the structure of amide **V** is its condensation with acetone, which also involves carbamoyl and thiocarbamoyl fragments of the molecule. As a result we obtained the first representative of the heterocyclic system of [1,3]thiazino[6,5-*c*]isoquinoline **IX**, whose structure was reliably confirmed by X-ray diffraction analysis (see the figure and the table), which, in turn, allows the unambiguous attribution to the condensation products of enamine **I** with monothiomalonodiamide **III** of the structure of 3-thioxoisoquinoline-4-carboxamide **V**.



Steric structure of compound **IX** according to XRD data.

The cyclohexane ring conformation in compound **IX** is a *semichair* with the C^6–C^4–C^3–C^9 planar fragment [torsion angle –1.70(18)°] and atoms C^7 and C^8 deviating from it by –0.451(3) and 0.318 Å,



II, IV, R = $PhCH_2$ (**a**), cyclo-C_3H_5 (**b**), 2-MeC_6H_4 (**c**), thiazol-2-yl (**d**), pyridin-2-yl (**e**); **VII, VIII**, X = H_2C=CH (**a**), HC≡C (**b**), 4-ClC_6H_4CO (**c**), 4-$NO_2C_6H_4CO$ (**d**).

respectively. The conformation of the thiazine ring is intermediate between a *sofa* and a *boat*. The fragment S^1–C^1–C^2–C^{16} is almost planar [torsion angle –6.30(16)°], the atoms N^2 and C^{17} deviate from this plane by 0.260(2) Å and 0.802 (2) Å, respectively. The repulsion between the aromatic ring and the nearest methylene group (short intramolecular contacts $H^{6b}\cdots C^{11}$ and $C^6\cdots C^{11}$, the sums of the van der Waals radii 2.87 and 3.42 Å [14], respectively) turns the phenyl substituent with respect to the plane of the pyridine ring by the torsion angle N^1–C^5–C^{10}–C^{15} 52.55(15)°.

In the crystal, the molecules form centrosymmetric dimers connected by hydrogen bonds between the amide groups N^2–$H^2\cdots O^1$ [–*x*, 1–*y*, –*z*] [H···O 2.063(14) Å, N–H···O 177.4(13)°]. The dimers form stacks along the (100) direction due to the hydrogen bond C^{11}–$H^{11}\cdots S^1$ [1 + *x*, *y*, *z*] (H···S 2.89 Å, C–H···S 163°), and weak C–H···π bonds C^8–$H^{8b}\cdots C^{16}$ [1 + *x*, *y*, *z*] (H···C 2.81 Å, C–H···C 166°) and C^7–$H^{7b}\cdots C^5$ [1 – *x*, –*y*, –*z*] (H···C 2.84 Å, C–H···C 159°).

EXPERIMENTAL

The crystals of compound **IX** are monoclinic, $C_{19}H_{20}N_2OS$, at 298 K α = 6.9586(6), *b* = 10.7905(9), *c* = 22.433(2) Å, β = 96.931(8)°, *V* = 1672.1(2) $Å^3$, M_r = 324.43, Z = 4, space group P, D_{calc} = 1.289 g cm^{-3},

μ(MoK_α) 0.200 mm^{-1}, F(000) 688. The unit cell parameters and intensities of 9713 reflections (5458 independent, R_{int} = 0.022) were measured on an automatic four-circle Xcalibur-3 diffractometer (MoK_α radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 65.18°).

The structure was solved by the direct method using the program package SHELX-97 [15]. The positions of the hydrogen atoms at the carbon atoms were calculated geometrically and refined using *rider* model with $U_{iso} = nU_{eq}$ of the host atom (n = 1.5 for methyl groups and n = 1.2 for the rest of hydrogen atoms). The position of the hydrogen atom at the N^2 was refined independently in the isotropic approximation. The structure was refined with respect to F^2 in a full-matrix anisotropic approximation for non-hydrogen atoms to wR_2 = 0.081 for 5458 reflections [R_1 = 0.041 for 2908 reflections with $F > 4\sigma(F)$, S = 0.99]. The bond lengths and bond angles are listed in the table.

Melting points of the synthesized compounds were determined on a Koeffler block. The IR spectra were recorded on a SPECTRUM ONE (Perkin Elmer) FTIR spectrometer from tablets with KBr. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer (500.068 and 125.7578 MHz, respectively) from the solutions in DMSO-d_6 (internal reference TMS). GC-MS spectra were recorded on a Crommas GC/MC Hewlett-Packard 5890/5972 instrument, column HP-S MS, 70 eV, solutions in CH_2Cl_2. The reaction progress and the purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in the system of acetone-hexane 3:5, developers iodine vapor and ultraviolet irradiation.

3-Oxo-1-phenyl-2-*R*-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles (IVa–IVe). To a stirred mixture of 2.71 g (10 mmol) of enaminoketone **I** and 10 mmol of a cyanoacetanilide **IIa–IIe** in 15 ml of anhydrous ethanol at 20ºC was added a solution of sodium ethoxide prepared from 0.23 g (10 mmol) of sodium and 10 mmol of anhydrous ethanol. The mixture was stirred for 1 h and left for a day. The resulting precipitate was filtered off, washed with ethanol, and crystallized.

2-Benzyl-3-oxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (IVa). Yield 2.31 g (68%), yellow powder, fluorescent under UV irradiation, mp 162–164°C (EtOH). IR spectrum, ν, cm^{-1}: 2211 (C≡N), 1647 (CONH). ^{1}H NMR spectrum, δ, ppm: 7.39–7.52 m (3H, Ph), 7.21 m (3H, Ph), 7.13 d (2H, Ph, J 6.64 Hz), 6.81 m (2H, Ph), 4.91 s (2H, NCH_2), 2.88 t (2H, CH_2, J 6.0 Hz), 1.96 t (2H, CH_2, J 6.4 Hz), 1.71 m (2H, CH_2), 1.55 m(2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 20.68 (CH_2), 21.66 (CH_2), 25.92 (CH_2), 28.88 (CH_2), 48.96 (CH_2), 100.69 (C^4), 115.06 (CN), 115.64 (C^6), 126.20, 127.00, 127.92, 128.17, 128.80, 129.48, 132.38, 136.25 (C_{arom}), 151.92 (C^1), 159.15 (C^3), 159.55 (C^5). Mass spectrum, *m/z* (I_{rel}, %): 341 (100) $[M + 1]^+$. Found, %: C 81.01, H 5.88, N 8.19. $C_{23}H_{20}N_2O$. Calculated, %: C 81.15, H 5.92, N 8.23.

3-Oxo-1-phenyl-2-cyclopropyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (IVb). Yield 2.26 g (78%), yellow crystals, fluorescent under UV irradiation, mp 142–144°C (EtOH). IR spectrum, ν, cm^{-1}: 2214 (C≡N), 1646 (CO). ^{1}H NMR spectrum, δ, ppm: 7.33–7.58 m (5H, Ph), 2.81 t (2H, CH_2, J 6.4 Hz), 2.77 m (1H, NCH), 1.69 m (2H, CH_2), 1.54 m (2H, CH_2), 0.61 m (2H, CH_2 cyclopropane), 0.51 m (2H, CH_2 cyclopropane). ^{13}C NMR spectrum, δ, ppm: 10.68 ($2CH_2$), 20.70 ($2CH_2$), 21.82 (CH_2), 25.84 (CH_2), 31.11 (CH), 100.86 (C^4), 114.45 (CN), 115.77 (C^6), 128.41, 128.58, 128.91, 133.39 (C_{arom}), 153.44 (C^1), 158.91 (C^3), 160.27 (C^5). Mass spectrum, *m/z* (I_{rel}, %): 291 (100) $[M + 1]^+$. Found, %: C 78.48, H 6.14, N 9.58. $C_{19}H_{18}N_2O$. Calculated, %: C 78.59, H 6.25, N 9.65.

3-Oxo-2-(*o*-tolyl)-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (IVc). Yield 82%, white powder, fluorescent under UV irradiation, mp 205–208°C (AcOH). IR spectrum, ν, cm^{-1}: 2219 (C≡N), 1652 (CONH). ^{1}H NMR spectrum, δ, ppm: 7.02–7.26 m (9H, H_{arom}) 2.98 t (2H, CH_2, J 6.0 Hz), 2.12 t (2H, CH_2, J 6.0 Hz), 1.81 m (2H, CH_2), 1.66 m (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 17.28 (CH_3), 20.71 (CH_2), 21.65 (CH_2), 25.89 (CH_2), 29.01 (CH_2), 100.97 (C^4), 114.78 (CN), 115.46 (C^6), 125.92, 126.65, 127.92, 128.39, 128.75, 129.26, 130.02, 132.51, 134.62, 137.04 (C_{arom}), 151.40 (C^1), 158.36 (C^3), 160.15 (C^5). Mass spectrum, *m/z* (I_{rel}, %): 341 (100) $[M + 1]^+$. Found, %: C 81.02, H 5.86, N 8.19. $C_{23}H_{20}N_2O$. Calculated, %: C 81.15, H 5.92, N 8.23.

3-Oxo-2-(thiazol-2-yl)-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (IVd). Yield 2.36 g (71%), yellow powder, fluorescent under UV irradiation, mp 257–259°C (BuOH). IR spectrum, ν, cm^{-1}: 2214 (C≡N), 1665 (CONH). ^{1}H NMR spectrum, δ, ppm: 7.71 d (1H, thiazole, J 3.2 Hz), 7.54 d (1H, thiazole, J 3.2 Hz), 7.22–7.31 m (5H, Ph), 2.96 t (2H,

CH_2, *J* 6.4 Hz), 2.11 t (2H, CH_2, *J* 6.8 Hz), 1.74 m (2H, CH_2), 1.61 m (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 20.58 (CH_2), 21.47 (CH_2), 25.63 (CH_2), 29.28 (CH_2), 101.44 (C^4), 114.85 (CN), 115.56 (C^6), 124.37, 128.03, 128.99, 129.09, 131.55, 139.92, 150.39 (C_{arom}), 156.74 (C^1), 158.89 (C^3), 162.35 (C^5). Mass spectrum, *m*/*z* (I_{rel}, %): 334 (100) $[M + 1]^+$. Found, %: C 68.33, H 4.48, N 12.52. $C_{19}H_{15}N_3OS$. Calculated, %: C 68.45, H 4.53, N 12.60.

3-Oxo-2-(pyridin-2-yl)-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (Ie). Yield 2.35 g (72%), white powder, fluorescent under UV irradiation, mp 235–238°C (BuOH). IR spectrum, ν, cm^{-1}: 2214 (C≡N), 1659 (CONH). ^1H NMR spectrum, δ, ppm: 8.33 m (1H, pyridine), 7.76 t (1H, pyridine, *J* 8.0 Hz), 7.41 d (1H, pyridine, *J* 8.0 Hz), 7.16–7.25 m (6H, Ph and pyridine), 2.95 m (2H, CH_2), 2.08 m (2H, CH_2), 1.76 m (2H, CH_2), 1.61 m (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 20.72 (CH_2), 21.64 (CH_2), 25.56 (CH_2), 29.12 (CH_2), 101.20 (C^4), 114.54 (CN), 115.29 (C^6), 123.79, 124.56, 127.95, 128.48, 128.74, 129.20, 132.05, 138.08, 148.75 (C_{arom}), 150.76 (C^1), 158.89 (C^3), 161.13 (C^5). Mass spectrum, *m*/*z* (I_{rel}, %): 328 (100) $[M + 1]^+$. Found, %: C 76.95, H 5.11, N 12.75. $C_{21}H_{17}N_3O$. Calculated, %: C 77.04, H 5.23, N 12.84.

3-Thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxamide (V). To a stirred solution of 2.71 g (10 mmol) of enaminoketone **I** in 15 ml of anhydrous ethanol at 20°C was added 1.2 g (10 mmol) monothiomalonodiamide **III** and a sodium ethoxide solution prepared from 0.23 g (10 mmol) of sodium and 10 mg of anhydrous ethanol. The mixture was stirred for 30 min and left for 2 days. The reaction mixture was diluted with 10% hydrochloric acid to pH 5 and left for one day. The resulting precipitate was filtered off and crystallized from ethanol. Yield 1.96 g (69%), yellow powder, mp 235–238°C. IR spectrum, ν, cm^{-1}: 3382, 3211 (NH, NH_2), 1678 (C=O), 1194 (C=S). ^1H NMR spectrum, δ, ppm: 7.31–7.48 m (6H, Ph and NH_2), 7.0 br.s (1H, NH_2), 2.6 t (2H, CH_2, *J* 6.0 Hz), 2.37 t (2H, CH_2, *J* 6.0 Hz), 1.63 m (2H, CH_2), 1.52 m (2H, CH_2). Proton signal of N^2H not observed, apparently due to rapid deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 21.11 (CH_2), 21.62 (CH_2), 25.34 (CH_2), 26.66 (CH_2), 120.56 (C^6), 128.28, 128.71, 129.05, 129.38 (C_{arom}), 132.42 (C^4), 138.95 (C^1), 144.95 (C^3), 146.93 (C^5), 168.14 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 285 (100) $[M + 1]^+$. Found, %: C 67.42, H 5.48, N 9.77. $C_{16}H_{16}N_2OS$. Calculated, %: C 67.58, H 5.67, N 9.85.

3-Methylthio-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxamides (VIIIa–VIIId). To a stirred solution of 2.84 g (10 mmol) of isoquinoline-3-thione **V** in 15 ml of DMF was added sequentially 5.6 ml (10 mmol) of 10% aqueous KOH and 10 mmol of an alkylating agent **VIIa–VIId.** The mixture was stirred for 1 h and left for one day. The reaction mixture was diluted with an equal amount of water and the resulting precipitate was filtered off, washed with water, ethanol, and crystallized.

3-Allylthio-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxamide (VIIIa). Yield 2.56 g (79%), mp 210–212°C (EtOH). IR spectrum, ν, cm^{-1}: 3378, 3177 (NH_2), 1642 (CONH). ^1H NMR spectrum, δ, ppm: 7.81 br.s (1H, NH_2), 7.60 br.s (1H, NH_2), 7.37–7.49 m (5H, Ph), 5.86–5.97 m (1H, =CH), 5.21 d (1H, $=CH_2$, J_{trans} 16.8 Hz), 5.03 d (1H,$=CH_2$, J_{cis} 9.6 Hz), 3.79 d (2H, SCH_2, *J* 6.8 Hz), 2.77 t (2H, CH_2, *J* 5.9 Hz), 2.66 t (2H, CH_2, *J* 5.9 Hz), 1.78 t (2H, CH_2), 1.67 t (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 21.29 (CH_2), 22.11 (CH_2), 25.98 (CH_2), 26.90 (CH_2), 32.04 (CH_2), 117.12 ($H_2C=$), 126.54 (C^4), 127.90, 128.68, 131.35, 134.55 (C_{arom}), 139.86 (=CH), 143.27 (C^5), 148.91 (C^3), 156.60 (C^1), 167.86 [C(O)NH_2]. Mass spectrum, *m*/*z* (I_{rel}, %): 325 (100) $[M + 1]^+$. Found, %: C 70.28, H 6.14, N 8.58. $C_{19}H_{20}N_2OS$. Calculated, %: C 70.34, H 6.21, N 8.63.

3-(Prop-2-inylthio)-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxamide (VIIIb). Yield 2.64 g (82%), mp 157–158°C (BuOH). IR spectrum, ν, cm^{-1}: 3392, 3112 (NH_2), 1666 (CONH). ^1H NMR spectrum, δ, ppm: 7.88 br.s (1H, NH_2), 7.66 br.s (1H, NH_2), 7.39–7.54 m (5H, Ph), 3.93 s (2H, SCH_2), 2.89 s (1H, ≡CH), 2.89 m (2H, CH_2, *J* 6.0 Hz), 2.70 m (2H, CH_2, *J* 6.0 Hz), 1.79 m (2H, CH_2), 1.68 m (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 323 (100) $[M + 1]^+$. Found, %: C 70.68, H 5.48, N 8.55. $C_{19}H_{18}N_2OS$. Calculated, %: C 70.78, H 5.63, N 8.69.

1-Phenyl-3-(4-chlorbenzoylmethylthio)-5,6,7,8-tetrahydroisoquinoline-4-carboxamide (VIIIc). Yield 3.31 g (76%), mp 225–228°C (AcOH). IR spectrum, ν, cm^{-1}: 3377, 3189 (NH_2), 1691 (C=O), 1636 (CONH). ^1H NMR spectrum, δ, ppm: 8.0 br.s (1H, NH_2), 7.92 d (2H, C_6H_4, *J* 8.5 Hz), 7.77 br.s (1H, NH_2), 7.45 d (2H, C_6H_4, *J* 8.5 Hz), 7.21–7.32 m (5H, Ph), 4.59 s (2H, SCH_2), 2.74 t (2H, CH_2, *J* 6.0 Hz), 2.58 t (2H, CH_2, *J* 6.0 Hz), 1.71 m (2H, CH_2), 1.56 m (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 21.19 (CH_2), 21.99 (CH_2), 25.96 (CH_2), 26.72 (CH_2), 36.14 (CH_2),

126.54 (C^4), 127.49, 127.52, 128.37, 129.90, 130.45, 135.05, 137.73, 139.08 (C_{arom}), 143.43 (C^6), 148.26 (C^3), 156.31 (C^1), 167.66 [C(O)NH_2], 193.85 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 437 (100) $[M + 1]^+$. Found, %: C 65.80, H 4.79, N 6.35. $C_{24}H_{21}ClN_2O_2S$. Calculated, %: C 65.97, H 4.84, N 6.41.

3-(4-Nitrobenzoylmetilthio)-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxamide (VIIId). Yield 3.13 g (70%), mp 215–217°C (BuOH). IR spectrum, ν, cm^{-1}: 3378, 3178, 2934 (NH_2), 1698 (C=O), 1640 (NHCO), 1603 (NO_2). ^1H NMR spectrum, δ, ppm: 8.09 d (2H, C_6H_4, *J* 8.0 Hz), 5.8 d (2H, C_6H_4, *J* 8.0 Hz), 7.93 br.s (1H, NH_2), 7.70 br.s (1H, NH_2), 7.15–7.33 m (5H, Ph), 4.58 s (2H, SCH_2), 2.79 m (2H, CH_2, *J* 6.0 Hz), 2.57 m (2H, CH_2, *J* 6.0 Hz), 1.76 t (2H, CH_2), 1.64 t (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 21.12 ($2CH_2$), 21.89 (CH_2), 25.93 (CH_2), 36.38 (CH_2), 123.12 (C^4), 126.62, 127.33, 127.42, 128.26, 129.13, 130.33, 138.88, 141.42 (C_{arom}), 143.50 (C^6), 148.06 (C^5), 149.38 (C^3), 156.41 (C^1), 167.56 [C(O)NH_2], 194.17 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 448 (100) $[M + 1]^+$. Found, %: C 64.30, H 4.64, N 9.28. $C_{24}H_{21}N_3O_4S$. Calculated, %: C 64.42, H 4.73, N 9.39.

3,3-Dimethyl-1-oxo-6-phenyl-1,2,7,8.9,10-hexahydro-3*H*-[1,3]thiazino[6,5-*c*]isoquinoline (IX). To a solution of 2.84 g (10 mmol) of compound **V** in 10 ml of acetone was added a drop of concentrated hydrochloric acid. The mixture was boiled for 10 min, filtered hot and the filtrate was left for 48 h. The resulting yellow precipitate was filtered off, washed with acetone, and crystallized from ethanol. Yield 2.43 g (75%), mp 195–197°C. IR spectrum, ν, cm^{-1}: 3166 (NH), 1658 (C=O). ^1H NMR spectrum, δ, ppm: 8.76 br.s (1H, NH), 7.41–7.52 m (5H, Ph), 2.65 t (2H, CH_2, *J* 5.9 Hz), 2.52 m (2H, CH_2), 1.76 m (2H, CH_2), 1.55–1.66 m (8H, CH_2 and 2Me). ^{13}C NMR spectrum, δ, ppm: 21.13 (CH_2), 21.42 (CH_2), 26.95 (CH_2), 27.79 (CH_2), 29.54 (CH_2), 58.74 [C(NH)S] , 121.27 (C^4), 127.79, 128.04, 128.48, 128.70 (C_{arom}), 139.13 (C^6), 150.26 (C^5), 155.24 (C^3), 159.52 (C^1), 164.33 (C=O) . Mass spectrum, *m*/*z* (I_{rel}, %): 325 (100) $[M + 1]^+$. Found, %: C 70.28, H 6.14, N 8.58. $C_{19}H_{20}N_2OS$. Calculated, %: C 70.34, H 6.21, N 8.63.

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