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Efficient Synthesis and Some Transformations of 1-Hydrazinyl-5,6,7,8-tetrahydroisoquinolines Involving Rearrangement of the Pyridine Ring

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Abstract—A procedure was developed for the synthesis of 1-hydrazinyl-3-arylamino-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles via recyclization of the pyridine ring in 3-amino-2-aryl-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitriles by the action of hydrazine hydrate. The recyclization products were converted to new heterocyclic systems, 7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*]isoquinolines and 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-5,6,7,8-tetrahydroisoquinolines, by reactions with triethyl orthoformate and acetylacetone, respectively. Treatment of 1-hydrazinyl-3-arylamino-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles with sodium azide in acetic acid gave 1-azido-3-arylamino-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles, and azide–tetrazole isomerism of the latter was studied. The state of the azide–tetrazole equilibrium was found to depend on the solvent polarity and substituent nature in the arylamino group. The structure of 5-(2-methoxyanilino)-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*]isoquinoline-6-carbonitrile was confirmed by X-ray analysis, and intermolecular hydrogen bonds were detected in its crystal structure. The synthesized compounds were evaluated for antimicrobial activity.

Keywords: 5,6,7,8-tetrahydroisoquinoline, triazolo[3,4-*a*]pyridines, 1-(pyrazol-1-yl)tetrahydroisoquinolines, azide–tetrazole tautomerism, rearrangement, antimicrobial activity.

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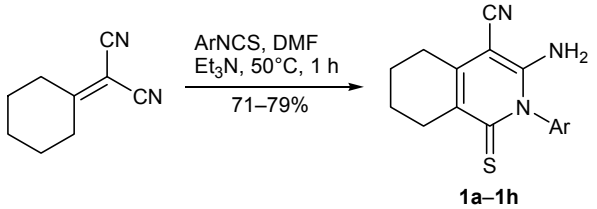
Increased interest in partially hydrogenated isoquinoline derivatives is related to the presence of an isoquinoline fragment in molecules of many alkaloids, as well as to the possibility of obtaining new biologically active compounds based thereon. Synthetic 1,2,3,4- and 5,6,7,8-tetrahydroisoquinoline derivatives were reported to exhibit antitumor, antimicrobial, antihypertensive, and neurotropic activities [1–5].

Syntheses of triazolopyridines and triazoloisoquinolines have been reported [6–8]. However, 7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*]isoquinoline derivatives have been poorly studied. We have found only two publications on the synthesis and biological activity of triazoloisoquinolines obtained from 5,6,7,8-tetrahydroisoquinoline derivatives [9, 10].

We previously described [11] recyclization of pyridine ring by the action of amines. Initially, we synthesized the corresponding pyridinium salts, and the latter were converted to 6,8-diaminopyrano[3,4-*c*]-pyridines. The goal of the present work was to synthesize 1-hydrazinyl-5,6,7,8-tetrahydroisoquinolines **2a**–**2h**. Unlike the rearrangement reported in [11], compounds **2a**–**2h** were obtained via recyclization of the pyridine ring in 3-amino-2-aryl-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitriles **1a**–**1h** by the action of hydrazine hydrate which is a strong nucleophile; we thus succeeded in reducing the number of steps. Initial hexahydroisoquinolinethiones **1a**–**1h** were prepared by reactions of cyclohexylidenemalononitrile with substituted phenyl isothiocyanates (Scheme 1). Compounds **2a**–**2h** were subjected to further transformations, which led to the formation of new heterocyclic systems. The synthesized compounds were evaluated for antimicrobial activity.

The reaction of **1a**–**1h** with hydrazine hydrate involved opening of the pyridine ring and subsequent recyclization accompanied by evolution of hydrogen

Scheme 1.



1a–1h

Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 2-$MeOC_6H_4$ (**e**), 3-$MeOC_6H_4$ (**f**), 4-$MeOC_6H_4$ (**g**), 4-ClC_6H_4 (**h**).

sulfide to afford 1-hydrazinyl derivatives **2a**–**2h** (Scheme 2). The mechanism of this rearrangement is likely to be similar to that proposed in [11]. Hydrazine molecule adds to the C^1 carbon atom, leading to cleavage of the C^1–N^2 bond. Rotation of the ArNH–C^3–NH_2 fragment in the intermediate thus formed is followed by pyridine ring closure with elimination of hydrogen sulfide.

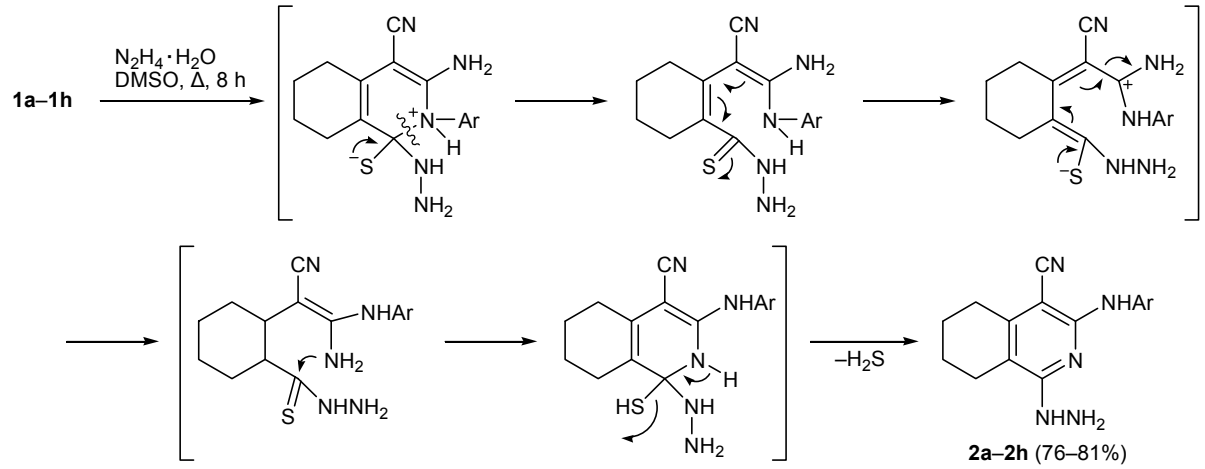
According to the data of [12], compound **2a** was synthesized by heating isoquinolinethione **1a** in hydrazine hydrate under reflux [12]. We used dimethyl sulfoxide as solvent and thus succeeded in improving the yield and shortening the reaction time.

The IR spectra of **2a**–**2h** showed absorption bands due to NH and NH_2 groups in the region 3150–3315 cm^{-1}, and the C≡N stretching band was observed at 2205–2209 cm^{-1}. In the ^{1}H NMR spectra of **2a**–**2h**, protons of the primary amino group resonated at δ 3.23–4.20 ppm, and signals at δ 7.15–7.75 and 7.69–8.21 ppm were assigned to protons of the NH groups linked to C^3 and C^1, respectively.

The reaction of hydrazinylisoquinolines **2a**–**2h** with triethyl orthoformate afforded 7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-*a*]isoquinolines **3a**–**3h** (Scheme 3). The IR spectra of **3a**–**3h** showed NH and C≡N stretching bands in the regions 3250–3335 and 2208–2216 cm^{-1}, respectively. In the ^{1}H NMR spectra of **3a**–**3h**, the 3-H proton resonated at δ 8.27–9.15 ppm, and the NH proton signal was observed at δ 9.32–9.77 ppm. The C^3 carbon signal of **3a**–**3h** was located at δ_C 133.6–140.0 ppm in the ^{13}C NMR spectra.

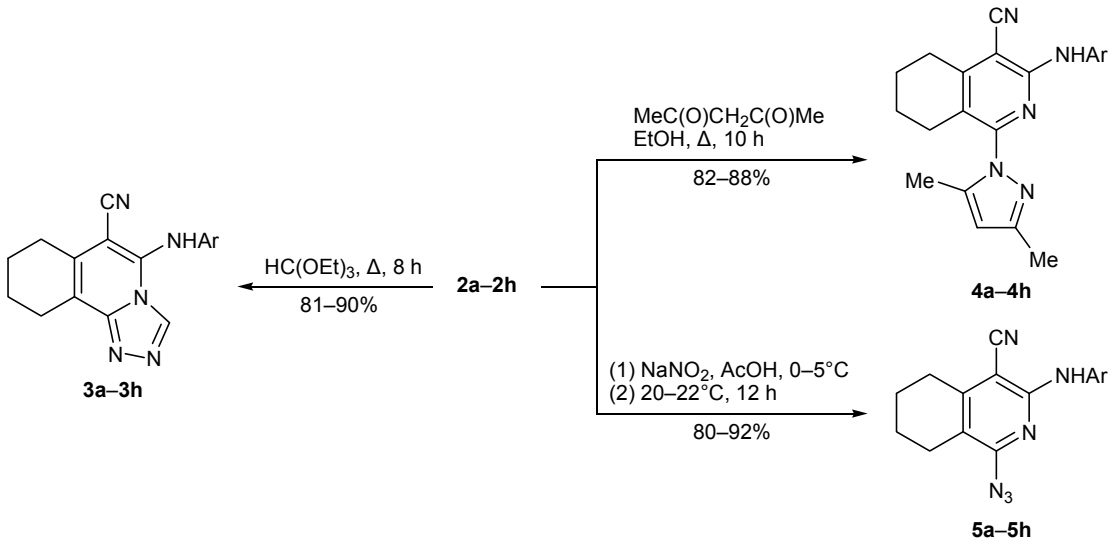
The X-ray diffraction study of a single crystal of **3b** confirmed the assigned structure. The cyclohexene ring in molecule **3b** has a clearly defined *half-chair* conformation where the C^1, C^4, C^5, and C^{13} atoms lie in one plane [the maximum deviation of atoms from the mean-square plane is 0.0601(2) Å] and the C^2 atom deviates from that plane by 0.7866(2) Å (Fig. 1). Analysis of the anisotropic thermal vibration ellipsoids and difference Fourier maps revealed statistical disordering of the C^2 and C^3 atoms by two positions whose populations were estimated at 38 and 62%. Molecules **3b** in crystal are linked through N^{16}–$H^{16}\cdots N^8$ intermolecular hydrogen bonds [$N^{16}\cdots N^8$ 2.919(4) Å] to form infinite chains along the [0 1 0] crystallographic direction (Fig. 2). These chains interact with each other mainly through van der Waals forces.

Scheme 2.



Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 2-$MeOC_6H_4$ (**e**), 3-$MeOC_6H_4$ (**f**), 4-$MeOC_6H_4$ (**g**), 4-ClC_6H_4 (**h**).

Scheme 3.



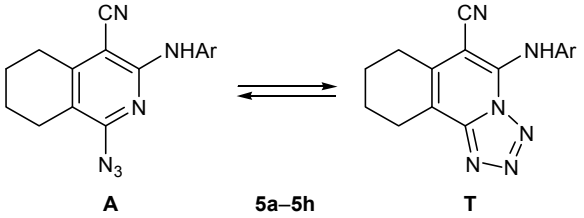
Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 2-$MeOC_6H_4$ (**e**), 3-$MeOC_6H_4$ (**f**), 4-$MeOC_6H_4$ (**g**), 4-ClC_6H_4 (**h**).

By reacting 1-hydrazinyl-5,6,7,8-tetrahydroisoquinolines **2a**–**2h** with acetylacetone we obtained 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-5,6,7,8-tetrahydroisoquinolines **4a**–**4h** (Scheme 3). The ^{1}H NMR spectra of **4a**–**4h** showed a signal at δ 5.23–5.91 ppm due to 4-H proton of the pyrazole ring, and the NH signal was located δ 7.85–8.90 ppm.

Treatment of hydrazines **2a**–**2h** with sodium nitrite in acetic acid at 0–5°C gave azido derivatives **5a**–**5h** (Scheme 3). The IR spectra of **5a**–**5h** characteristically displayed strong absorption bands in the region 2129–2137 cm^{-1} due to the azido group. The stability of the azido group in crystalline compounds **5a**–**5h** may be rationalized by electron-withdrawing effect of the cyano group, as well as by steric effect of the arylamino group in the 3-position, which hampers ring closure with participation of the pyridine nitrogen atom to form a tetrazole ring.

It is known that unsubstituted tetrazolo[1,5-*a*]pyridine in the crystalline state has cyclic structure which retains in polar and nonpolar solvents. Introduction of electron-withdrawing substituents into the cyclic system give rise to equilibrium in solution between isomeric tetrazole and azide structures [13–16].

Scheme 4.



The azide–tetrazole equilibrium of compounds **5a**–**5g** in solution (Scheme 4) was studied by ^{1}H NMR. Fused tetrazole ring is a stronger electron acceptor than azido group; therefore, protons of the tetrazole tautomer resonated in a weaker field than those of the corresponding azido tautomer. The fractions of the azide and tetrazole forms of **5a**–**5h** were estimated from the intensities of the NH and CH_2 proton signals.

Compounds **5a**–**5h** in $CDCl_3$ exist exclusively as azido tautomers, whereas equilibrium between the

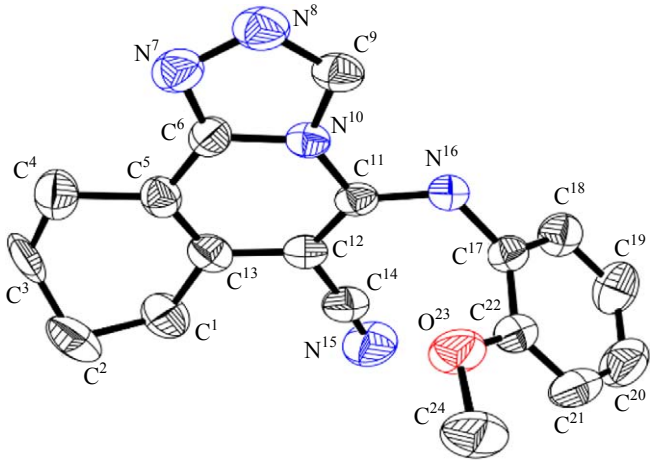


Fig. 1. Structure of the molecule of 5-(2-methylanilino)-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*]isoquinoline-6-carbonitrile (**3b**) according to the X-ray diffraction data. Nonhydrogen atoms are shown as anisotropic thermal vibration ellipsoids with a probability of 50%.

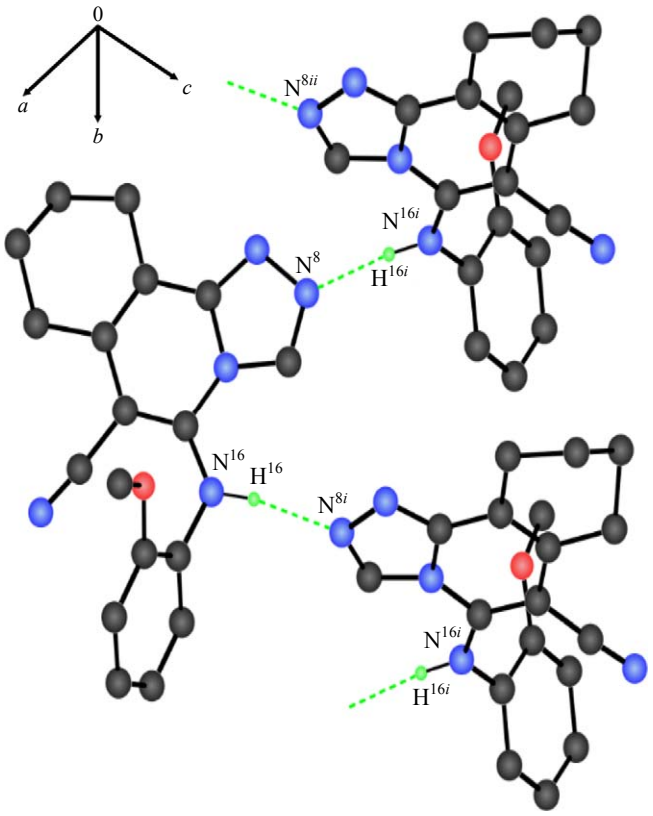


Fig. 2. Infinite chain formed by molecules **3b** in crystal through intermolecular hydrogen bonds along the [010] crystallographic direction; symmetry operations: *i*: –*x*, 0.5 + *y*, 0.5 – *z*; *ii*: –*x*, –0.5 + *y*, 0.5 – *z*. Hydrogen bonds are shown with dashed lines.

azide (**A**) and tetrazole (**T**) structures was observed in solutions in DMSO-d_6 and DMSO-d_6–CCl_4 (1:3). The tautomer ratio depended on the solvent polarity and substituent on C^3 (Table 1). The fraction of tautomer **T** in DMSO-d_6–CCl_4 (1:3) varied from 7 to 35%, depending on the substituent in the aniline fragment. In going to DMSO-d_6, the fraction of tetrazole tautomer increased to 35–78%. The presence of an electron-withdrawing chlorine atom in the benzene ring considerably reduced the fraction of tautomer **T** in comparison to the unsubstituted analog (R = H). By contrast, electron-donating groups (R = Me, MeO) in the benzene ring shifted the equilibrium toward the tetrazole tautomer. The position of the NH signal of both tautomers insignificantly depended on the substituent in the benzene ring (Table 2), but it strongly changed upon variation of the solvent.

It is known that tetrahydroisoquinoline derivatives exhibit pronounced antimicrobial activity [1, 5]. Therefore, all compounds synthesized in this work were evaluated for antimicrobial activity against gram-positive (*Staphylococcus aureus* 209p) and gram-negative bacteria (*Sh. Flexneri* 6858, *E. coli* 0-55) by the agar diffusion method [17]. Triazolo[3,4-*a*]isoquinolines **3a**–**3h** showed weak activity against all bacterial strains tested (d = 10–15 mm). Pyrazole derivatives **4a**–**4h** were equally active only against gram-negative bacteria. Azido derivatives **5a**–**5h** displayed a moderate antimicrobial activity against all test cultures (d = 16–20 mm). All compounds were inferior to furazolidone (d = 24–25 mm) [18].

In summary, an efficient procedure has been developed for the synthesis of 1-hydrazinyl-5,6,7,8-tetrahydroisoquinolines by recyclization of the pyridine ring in 3-amino-1,2,5,6,7,8-hexahydroisoquinoline-1-thiones. The synthesized compounds have been used to obtain new heterocyclic systems containing a tetrahydroisoquinoline fragment. Study of the azide–tetrazole tautomerism of 1-azido-5,6,7,8-tetrahydroisoquinolines in solution has shown that increase of the solvent polarity leads to increase of the fraction of the

Table 1. Fractions (%) of azide (**A**) and tetrazole (**T**) tautomers of 3-(arylamino)-1-azido-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles **5a**–**5h** in different solvents at 30°C

Compound no.	Ar	$CDCl_3$		DMSO-d_6–CCl_4, 1:3		DMSO-d_6	
		A	**T**	**A**	**T**	**A**	**T**
5a	Ph	100	–	87	13	55	45
5b	2-MeC_6H_4	100	–	65	35	22	78
5c	3-MeC_6H_4	100	–	88	12	44	56
5d	4-MeC_6H_4	100	–	85	15	50	50
5e	2-$MeOC_6H_4$	100	–	89	11	42	58
5f	3-$MeOC_6H_4$	100	–	90	10	59	41
5g	4-$MeOC_6H_4$	100	–	92	8	64	36
5h	4-ClC_6H_4	100	–	93	7	65	35

Table 2. Chemical shifts (δ, ppm) of the NH protons of the azide and tetrazole (**A**/**T**) tautomers of **5a**–**5h** in different solvents

Compound no.	$CDCl_3$	DMSO-d_6–CCl_4, 1:3	DMSO-d_6
5a	6.92/–	8.61/10.55	9.00/10.51
5b	6.78/–	7.97/10.33	8.54/10.34
5c	6.83/–	8.42/10.44	8.90/10.44
5d	6.86/–	8.42/10.41	8.88/10.43
5e	7.79/–	7.80/10.21	7.99/10.31
5f	6.93/–	8.53/10.47	8.96/10.48
5g	6.78/–	8.67/10.54	8.83/10.36
5h	6.90/–	8.85/10.60	9.18/10.58

tetrazole form. The tautomer ratio also depends on the substituent in the benzene ring of the arylamino group on C^3. Some of the synthesized compounds showed a moderate antimicrobial activity.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Avatar 330 FT-IR spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 VX instrument at 300 and 75.462 MHz, respectively, using tetramethylsilane as internal standard. Signals in the ^1H and ^{13}C NMR spectra were assigned with the aid of DEPT, NOESY (mixing time 1 s), and HMQC experiments. The elemental analyses were obtained on a Euro EA 3000 elemental analyzer. The melting points were measured on a Boetius hot stage. The crystallographic data for compound **3b** were deposited to the Cambridge Crystallographic Data Centre (CCDC no. 1574713). The structure of **3b** was determined by the direct method and was refined using SHELXTL software package [19].

Compounds 1a–1h (*general procedure*). Triethylamine, 1 mL, was added dropwise with stirring to a solution of 1.5 g (10 mmol) of cyclohexylidenemalononitrile and 10 mmol of substituted phenyl isothiocyanate in 2 mL of DMF. The mixture was stirred for 1 h at 50°C, cooled to room temperature, and diluted with 4 mL of methanol. The precipitate was filtered off, washed with water, and recrystallized from nitromethane.

3-Amino-2-phenyl-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1a) [12]**.** Yield 2.252 g (78%), mp 270–271°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.75–1.81 m (4H, 6-H, 7-H), 2.52–2.58 m (2H, 8-H), 2.67–2.73 m (2H, 5-H), 6.21 br.s (2H, NH_2), 7.10–7.15 m (2H, H_{arom}), 7.46–7.52 m (1H, H_{arom}), 7.55–7.63 m (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2, 22.4, 28.3, 28.5, 78.6, 115.6, 126.5, 127.9, 128.8, 130.0, 138.7, 144.4, 153.2, 181.9. Found, %: C 68.22; H 5.40; N 14.84; S 11.47. $C_{16}H_{15}N_3S$. Calculated, %: C 68.30; H 5.37; N 14.93; S 11.40.

3-Amino-2-(2-methylphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1b). Yield 2.243 g (74%), mp 243–245°C. IR spectrum, ν, cm^{-1}: 3451, 3308, 3211 (NH_2), 2205 (CN), 1623 (C=C), 1237 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.75–1.83 m (4H, 6-H, 7-H), 2.06 s (*3*H, CH_3), 2.53–2.59 m (2H, 8-H), 2.66–2.73 m (2H, 5-H), 6.21 br.s (2H, NH_2), 6.99–7.04 m (1H, H_{arom}), 7.37–7.41 m (3H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 16.7, 21.2, 22.3, 28.2, 28.4, 78.3, 115.5, 126.3, 127.5, 127.6, 129.0, 131.5, 134.9, 137.4, 144.3, 152.7, 180.8. Found, %: C 69.21; H 5.74; N 14.08; S 10.77. $C_{17}H_{17}N_3S$. Calculated, %: C 69.12; H 5.80; N 14.22; S 10.77.

3-Amino-2-(3-methylphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1c). Yield 2.273 g (75%), mp 239–241°C. IR spectrum, ν, cm^{-1}: 3445, 3317, 3215 (NH_2), 2206 (CN), 1627 (C=C), 1238 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.72–1.83 m (4H, 6-H, 7-H), 2.45 s (3H, CH_3), 2.52–2.58 m (2H, 8-H), 2.64–2.72 m (2H, 5-H), 6.20 br.s (2H, NH_2), 6.89–6.94 m (2H, H_{arom}), 7.29 d (1H, H_{arom}, J = 7.6 Hz), 7.31 t (1H, H_{arom}, J = 7.6 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.8, 21.2, 22.4, 28.2, 28.4, 78.4, 115.6, 124.8, 126.3, 128.2, 129.5, 129.7, 138.5, 139.6, 144.2, 153.1, 181.8. Found, %: C 69.35; H 5.76; N 14.28; S 10.74. $C_{17}H_{17}N_3S$. Calculated, %: C 69.12; H 5.80; N 14.22; S 10.85.

3-Amino-2-(4-methylphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1d). Yield 2.182 g (72%), mp 247–249°C. IR spectrum, ν, cm^{-1}: 3392, 3306, 3214 (NH_2), 2205 (CN), 1619 (C=C), 1237 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.74–1.82 m (4H, 6-H, 7-H), 2.47 s (3H, CH_3), 2.52–2.57 m (2H, 8-H), 2.66–2.71 m (2H, 5-H), 6.20 br.s (2H, NH_2), 6.97–7.02 m (2H, H_{arom}), 7.35–7.39 m (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.8, 21.2, 22.4, 28.2, 28.5, 78.5, 115.6, 126.3, 127.5, 130.6, 136.0, 138.2, 144.3, 153.3, 182.0. Found, %: C 69.02; H 5.74; N 14.36; S 10.91. $C_{17}H_{17}N_3S$. Calculated, %: C 69.12; H 5.80; N 14.22; S 10.85.

3-Amino-2-(2-methoxyphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1e). Yield 2.268 g (71%), mp 296–297°C. IR spectrum, ν, cm^{-1}: 3454, 3310, 3219 (NH_2), 2209 (CN), 1628 (C=C), 1239 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.74–1.82 m (4H, 6-H, 7-H), 2.52–2.58 m (2H, 8-H), 2.66–2.71 m (2H, 5-H), 3.81 s (3H, OCH_3), 6.24 br.s (2H, NH_2), 7.02 d.d (1H, H_{arom}, J = 7.8, 1.8 Hz), 7.11 d.d.d (1H_{arom}, J = 7.8, 7.3, 1.1 Hz), 7.16 d.d (1H, H_{arom}, J = 8.4, 1.1 Hz), 7.46 d.d.d (1H, H_{arom}, J = 8.4, 7.3, 1.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2, 22.4, 28.2, 28.5, 55.3, 78.1, 113.0, 115.8, 121.3, 126.0, 126.7, 128.9, 130.4, 144.2, 153.2, 153.8, 181.7. Found, %: C 65.48; H 5.57; N 13.34; S 10.37. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.49; S 10.30.

3-Amino-2-(3-methoxyphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1f). Yield 2.396 g (75%), mp 218–220°C. IR spectrum, ν, cm^{-1}: 3451, 3308, 3215 (NH_2), 2208 (CN), 1621 (C=C), 1234 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.73–1.83 m (4H, 6-H, 7-H), 2.52–2.58 m (2H, 8-H), 2.64–2.71 m (2H, 5-H), 3.84 s (3H, OCH_3), 6.31 br.s (2H, NH_2), 6.66–6.71 m (2H, H_{arom}), 6.99–7.04 m (1H, H_{arom}), 7.44–7.51 m (1H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2, 22.4, 28.2, 28.4, 54.8, 78.5, 113.4, 114.8, 115.6, 119.6, 126.2, 130.6, 139.5, 144.3, 153.2, 160.7, 181.7. Found, %: C 65.68; H 5.44; N 13.57; S 10.22. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.49; S 10.30.

3-Amino-2-(4-methoxyphenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1g). Yield 2.332 g (73%), mp 252–254°C. IR spectrum, ν, cm^{-1}: 3455, 3312, 3223 (NH_2), 2209 (CN), 1631 (C=C), 1236 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.73–1.82 m (4H, 6-H, 7-H), 2.52–2.57 m (2H, 8-H), 2.65–2.70 m (2H, 5-H), 3.89 s (3H, OCH_3), 6.27 br.s (2H, NH_2), 6.98–7.03 m (2H, H_{arom}), 7.06–7.10 m (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2, 22.4, 28.2, 28.4, 54.8, 78.4, 115.2, 115.7, 126.2, 128.9, 131.1, 144.3, 153.6, 159.3, 182.4. Found, %: C 65.51; H 5.56; N 13.41; S 10.18. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.49; S 10.30.

3-Amino-2-(4-chlorophenyl)-1-sulfanylidene-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (1h). Yield 2.560 g (79%), mp 256–258°C. IR spectrum, ν, cm^{-1}: 3465, 3327, 3212 (NH_2), 2206 (CN), 1624 (C=C), 1238 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.71–1.83 m (4H, 6-H, 7-H), 2.51–2.57 m (2H, 8-H), 2.65–2.73 m (2H, 5-H), 6.54 br.s (2H, NH_2), 7.07–7.14 m (2H, H_{arom}), 7.52–7.58 m (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2, 22.4, 28.3, 28.4, 78.6, 115.6, 126.1, 129.8, 130.2, 133.9, 137.4, 144.8, 153.3, 181.8. Found, %: C 65.91; H 4.54; N 13.18; S 10.23. $C_{16}H_{14}ClN_3S$. Calculated, %: C 60.85; H 4.47; N 13.31; S 10.15.

Compounds 2a–2h (*general procedure*). A mixture of 10 mmol of compound **1a**–**1h** and 10 mL of hydrazine hydrate in 5 mL of DMSO was refluxed for 8 h. The mixture was cooled to room temperature, and the precipitate was filtered off, washed with water, dried, and recrystallized from dioxane.

3-Anilino-1-hydrazinyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2a) [12]**.** Yield 2.207 g (79%), mp 238–239°C. IR spectrum, ν, cm^{-1}: 3440, 3320, 3234 (NH, NH_2), 2206 (CN), 1611 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.74–1.83 m (4H, 6-H, 7-H), 2.22–2.29 m (2H, 8-H), 2.64–2.70 m (2H, 5-H), 4.27 br.s (2H, NH_2), 6.87–6.93 m (1H, H_{arom}), 7.18–7.24 m (2H, H_{arom}), 7.58–7.63 m (2H, H_{arom}), 7.76 br.s (1H, NH), 7.92 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.4, 21.5, 21.7, 27.6, 79.3, 106.6, 117.1, 120.1, 121.0, 127.6, 140.1, 147.2, 154.5, 157.7. Found, %: C 68.87; H 6.08; N 25.19. $C_{16}H_{17}N_5$. Calculated, %: C 68.79; H 6.13; N 25.07.

1-Hydrazinyl-3-(2-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2b). Yield 2.392 g (81%), mp 182–183°C. IR spectrum, ν, cm^{-1}: 3445, 3318, 3231 (NH, NH_2), 2205 (CN), 1617 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.73–1.83 m (4H, 6-H, 7-H), 2.20–2.27 m (2H, 8-H), 2.30 s (3H, CH_3), 2.64–2.69 m (2H, 5-H), 4.00 br.s (2H, NH_2), 6.94 d.d.d (1H, H_{arom}, J = 8.4, 7.8, 1.1 Hz), 7.09–7.17 m (3H, NH, H_{arom}), 7.69 br.s (1H, NH),

7.77 d (1H, H_{arom}, J = 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 17.6, 21.3, 21.4, 21.7, 27.6, 78.3, 106.0, 117.3, 122.8, 123.0, 125.4, 129.4, 129.5, 137.9, 146.8, 155.2, 157.8. Found, %: C 69.74; H 6.49; N 23.82. $C_{17}H_{19}N_5$. Calculated, %: C 69.60; H 6.53; N 23.87.

1-Hydrazinyl-3-(3-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2c). Yield 2.304 g (78%), mp 204–205°C. IR spectrum, ν, cm^{-1}: 3440, 3325, 3218 (NH, NH_2), 2208 (CN), 1626 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.74–1.82 m (4H, 6-H, 7-H), 2.23–2.28 m (2H, 8-H), 2.32 s (3H, CH_3), 2.64–2.69 m (2H, 5-H), 4.18 br.s (2H, NH_2), 6.71 br.d (1H, H_{arom}, J = 7.5 Hz), 7.09 d.d (1H, H_{arom}, J = 8.8, 7.5 Hz), 7.39–7.44 m (2H, H_{arom}), 7.75 br.s (1H, NH), 7.76 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.0, 21.4, 21.5, 21.7, 27.6, 79.1, 106.4, 117.2, 120.6, 121.9, 127.5, 136.8, 140.0, 147.1, 154.5, 157.8. Found, %: C 69.68; H 6.57; N 23.79. $C_{17}H_{19}N_5$. Calculated, %: C 69.60; H 6.53; N 23.87.

1-Hydrazinyl-3-(4-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2d). Yield 2.245 g (76%), mp 219–220°C. IR spectrum, ν, cm^{-1}: 3437, 3309, 3200 (NH, NH_2), 2205 (CN), 1631 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.73–1.82 m (4H, 6-H, 7-H), 2.21–2.28 m (2H, 8-H), 2.30 s (3H, CH_3), 2.63–2.68 m (2H, 5-H), 4.13 br.s (2H, NH_2), 6.99–7.05 m (2H, H_{arom}), 7.43–7.48 m (2H, H_{arom}), 7.70 br.s (1H, NH), 7.77 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.3, 21.4, 21.5, 21.7, 27.6, 78.7, 106.2, 117.3, 120.5, 128.2, 130.1, 137.5, 147.1, 154.7, 157.8. Found, %: C 69.54; H 6.51; N 23.92. $C_{17}H_{19}N_5$. Calculated, %: C 69.60; H 6.53; N 23.87.

1-Hydrazinyl-3-(2-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2e). Yield 2.382 g (77%), mp 233–234°C. IR spectrum, ν, cm^{-1}: 3443, 3312, 3218 (NH, NH_2), 2206 (CN), 1630 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.74–1.84 m (4H, 6-H, 7-H), 2.24–2.29 m (2H, 8-H), 2.65–2.70 m (2H, 5-H), 3.96 s (3H, OCH_3), 4.20 br.s (2H, NH_2), 6.86–6.94 m (3H, H_{arom}), 7.51 br.s (1H, NH), 7.72 br.s (1H, NH), 8.45–8.50 m (1H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.3, 21.5, 21.7, 27.5, 55.4, 79.0, 106.1, 109.5, 117.0, 118.5, 120.2, 120.7, 129.1, 146.7, 147.4, 154.2, 158.2. Found, %: C 65.94; H 6.23; N 22.69. $C_{17}H_{19}N_5O$. Calculated, %: C 66.00; H 6.19; N 22.64.

1-Hydrazinyl-3-(3-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2f). Yield 2.475 g (80%), mp 193–194°C. IR spectrum, ν, cm^{-1}: 3445, 3315, 3216 (NH, NH_2), 2208 (CN), 1629 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.74–1.83 m (4H, 6-H, 7-H), 2.23–2.28 m (2H, 8-H), 2.64–2.69 m (2H, 5-H), 3.76 s (3H, OCH_3), 4.18 br.s (2H, NH_2), 6.44 d.d.d (1H, H_{arom}, J = 8.0, 2.6, 1.1 Hz), 7.08 t (1H, H_{arom}, J = 8.0 Hz), 7.15 d.d.d (1H, H_{arom}, J = 8.0, 1.8, 1.1 Hz), 7.34 d.d (1H, H_{arom}, J = 2.6, 1.8 Hz), 7.77 br.s (1H, NH), 7.90 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.4, 21.5, 21.7, 27.6, 54.4, 79.3, 105.3, 106.6, 107.1, 112.2, 117.1, 128.2, 141.4, 147.1, 154.4, 157.7, 159.2. Found, %: C 66.08; H 6.24; N 22.58. $C_{17}H_{19}N_5O$. Calculated, %: C 66.00; H 6.19; N 22.64.

1-Hydrazinyl-3-(4-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2g). Yield 2.444 g (79%), mp 193–194°C. IR spectrum, ν, cm^{-1}: 3444, 3311, 3215 (NH, NH_2), 2206 (CN), 1627 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.73–1.83 m (4H, 6-H, 7-H), 2.23–2.28 (2H, 8-H), 2.63–2.69 m (2H, 5-H), 3.23 br.s (2H, NH_2), 3.77 s (3H, OCH_3), 6.75–6.81 m (2H, H_{arom}), 7.45–7.50 m (2H, H_{arom}), 7.76 br.s (1H, NH), 7.80 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.4, 21.5, 21.7, 27.6, 54.6, 78.8, 106.0, 112.9, 117.2, 122.3, 132.0, 147.4, 154.4, 154.8, 157.4. Found, %: C 66.12; H 6.15; N 22.71. $C_{17}H_{19}N_5O$. Calculated, %: C 66.00; H 6.19; N 22.64.

3-(4-Chloroanilino)-1-hydrazinyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (2h). Yield 2.486 g (78%), mp 218–219°C. IR spectrum, ν, cm^{-1}: 3439, 3317, 3220 (NH, NH_2), 2209 (CN), 1630 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.72–1.83 m (4H, 6-H, 7-H), 2.22–2.30 m (2H, 8-H), 2.63–2.70 m (2H, 5-H), 4.14 br.s (2H, NH_2), 7.15–7.20 m (2H, H_{arom}), 7.61–7.67 m (2H, H_{arom}), 7.75 br.s (1H, NH), 8.21 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 21.4, 21.5, 21.7, 27.6, 79.5, 106.9, 117.0, 121.5, 125.2, 127.4, 139.1, 147.3, 154.2, 157.7. Found, %: C 61.29; H 5.17; N 22.28. $C_{16}H_{16}ClN_5$. Calculated, %: C 61.24; H 5.14; N 22.32.

Compounds 3a–3h (*general procedure*). A mixture of 5 mmol of compound **2a**–**2h** and 40 mL of triethyl orthoformate was refluxed for 8 h. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, dried, and recrystallized from ethanol–chloroform (1:1).

5-Anilino-7,8,9,10-tetrahydro[1,2,4]triazolo-[3,4-*a*]isoquinoline-6-carbonitrile (3a). Yield 1.258 g (87%), mp 288–290°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 2207 (CN), 1615 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.85–1.98 m (4H, 8-H, 9-H), 2.71–2.78 m (2H, 10-H), 2.89–2.97 m (2H, 7-H), 7.01–7.14 m (3H, H_{arom}), 7.29-7.37 m (2H, H_{arom}), 8.93 s (1H, 3-H), 9.68 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C: 20.9, 21.7, 22.9, 26.8, 85.4, 114.0, 115.8, 120.4, 123.5, 128.7, 134.0, 134.3, 138.8, 139.4, 148.6. Found, %: C 70.65; H 5.19; N 24.14. $C_{17}H_{15}N_5$. Calculated, %: C 70.57; H 5.23; N 24.21.

5-(2-Methylanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3b). Yield 1.229 g (81%), mp 193–195°C. IR spectrum, ν, cm^{-1}: 3401 (NH), 2207 (CN), 1612 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.81–1.93 m (4H, 8-H, 9-H), 2.29 s (3H, CH_3), 2.68–2.73 m (2H, 10-H), 2.84–2.89 m (2H, 7-H), 7.19–7.28 m (4H, H_{arom}), 8.29 s (1H, 3-H), 9.32 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 17.5, 21.0, 21.8, 22.9, 27.2, 78.3, 112.7, 113.1, 125.8, 127.3, 127.6, 130.0, 135.3, 135.7, 139.0, 143.1, 150.5, 153.1. Found, %: C 71.35; H 5.61; N 22.98. $C_{18}H_{17}N_5$. Calculated, %: C 71.27; H 5.65; N 23.09.

5-(3-Methylanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3c). Yield 1.289 g (85%), mp 257–258°C. IR spectrum, ν, cm^{-1}: 3393 (NH), 2205 (CN), 1610 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.85–1.98 m (4H, 8-H, 9-H), 2.36 s (3H, CH_3), 2.72–2.78 m (2H, 10-H), 2.91–2.97 m (2H, 7-H), 6.79–6.85 m (2H, H_{arom}), 6.91 br.d (1H, H_{arom}, J = 7.6 Hz), 7.20 t (1H, H_{arom}, J = 7.6 Hz), 8.88 s (1H, 3-H), 9.61 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.8, 20.9, 21.7, 22.9, 26.8, 85.3, 114.0, 115.6, 117.5, 120.9, 124.3, 128.5, 133.9, 134.3, 138.1, 138.6, 139.3, 148.6. Found, %: C 71.32; H 5.69; N 23.15. $C_{18}H_{17}N_5$. Calculated, %: C 71.27; H 5.65; N 23.09.

5-(4-Methylanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3d). Yield 1.335 g (88%), mp 242–244°C. IR spectrum, ν, cm^{-1}: 3386 (NH), 2206 (CN), 1605 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.82–1.95 m (4H, 8-H, 9-H), 2.39 s (3H, CH_3), 2.73–2.79 m (2H, 10-H), 2.85–2.92 m (2H, 7-H), 7.09–7.16 m (4H, H_{arom}), 8.27 s (1H, 3-H), 9.48 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.5, 21.0, 21.8, 23.0, 27.2, 80.6, 113.6, 113.7, 123.8, 128.7, 134.2, 134.8, 138.8, 142.4, 150.7, 153.1. Found, %: C 71.21; H 5.68; N 23.17. $C_{18}H_{17}N_5$. Calculated, %: C 71.27; H 5.65; N 23.09.

5-(2-Methoxyanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3e). Yield 1.373 g (86%), mp 263–264°C. IR spectrum, ν, cm^{-1}: 3405 (NH), 2208 (CN), 1608 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.82–1.94 m (4H, 8-H, 9-H), 2.64–2.70 m (2H, 10-H), 2.88–2.93 m (2H, 7-H), 3.84 s (3H, OCH_3), 6.95 t.d (1H, H_{arom}, J = 7.7, 1.3 Hz), 7.03 d.d (1H, H_{arom}, J = 8.3, 1.3 Hz), 7.15 d.d (1H, H_{arom}, J = 7.7, 1.6 Hz), 7.24 d.d.d (1H, H_{arom}, J = 8.3, 7.7, 1.6 Hz), 9.15 s (1H, 3-H), 9.34 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.9, 21.8, 22.8, 26.8, 55.1, 81.1, 111.4, 113.3, 113.9, 120.2, 125.1, 126.0, 126.8, 133.6, 134.6, 140.5, 148.4, 153.2. Found, %: C 67.78; H 5.34; N 21.81. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

5-(3-Methoxyanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3f). Yield 1.389 g (87%), mp 268–269°C. IR spectrum, ν, cm^{-1}: 3395 (NH), 2207 (CN), 1612 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.85–1.98 m (4H, 8-H, 9-H), 2.73–2.79 m (2H, 10-H), 2.89–2.97 m (2H, 7-H), 3.79 s (3H, OCH_3), 6.53–6.67 m (3H, H_{arom}), 7.20 t (1H, H_{arom}, J = 8.1 Hz), 8.89 s (1H, 3-H), 9.67 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.8, 21.7, 22.9, 26.8, 54.6, 86.1, 106.1, 109.0, 112.2, 114.0, 116.1, 129.4, 134.0, 134.3, 139.1, 140.0, 148.6, 159.8. Found, %: C 67.81; H 5.31; N 21.84. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

5-(4-Methoxyanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3g). Yield 1.437 g (90%), mp 214–216°C. IR spectrum, ν, cm^{-1}: 3402 (NH), 2208 (CN), 1609 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.83–1.94 m (4H, 8-H, 9-H), 2.64–2.70 m (2H, 10-H), 2.86–2.91 m (2H, 7-H), 3.82 s (3H, OCH_3), 6.87–6.97 m (2H, H_{arom}), 7.07–7.12 m (2H, H_{arom}), 9.07 s (1H, 3-H), 9.52 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.9, 21.8, 22.7, 26.8, 54.8, 81.0, 113.5, 113.9, 114.1, 124.7, 130.7, 133.6, 134.8, 140.9, 148.5, 156.9. Found, %: C 67.77; H 5.43; N 22.05. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

5-(4-Chloroanilino)-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*]isoquinoline-6-carbonitrile (3h). Yield 1.408 g (87%), mp 227–229°C. IR spectrum, ν, cm^{-1}: 3296 (NH), 2216 (CN), 1618 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.83–1.98 m (4H,

8-H, 9-H), 2.70–2.78 m (2H, 10-H), 2.89–2.98 m (2H, 7-H), 7.00–7.08 m (2H, H_{arom}), 7.28–7.34 m (2H, H_{arom}), 8.99 s (1H, 3-H), 9.77 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.8, 21.7, 22.9, 26.8, 85.9, 114.0, 116.2, 121.5, 127.8, 128.6, 134.0, 134.3, 137.8, 139.1, 148.6. Found, %: C 63.15; H 4.31; N 21.70. $C_{17}H_{14}ClN_5$. Calculated, %: C 63.06; H 4.36; N 21.63.

Compounds 4a–4h (*general procedure*). A mixture of 2 mmol of compound **2a**–**2h** and 0.40 g (4 mmol) of pentane-2,4-dione in 15 mL of anhydrous ethanol was refluxed for 10 h. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, dried, and recrystallized from ethanol.

3-Anilino-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4a). Yield 576.9 mg (84%), mp 206–207°C. IR spectrum, ν, cm^{-1}: 3405 (NH), 3126 (C–H), 2210 (CN), 1627 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.67–1.76 m (2H, 7-H), 1.83–1.92 m (2H, 6-H), 2.17 d (3H, CH_3, J = 0.6 Hz), 2.19 s (3H, CH_3), 2.57–2.62 m (2H, 8-H), 2.92–2.97 m (2H, 5-H), 5.85 br.s (1H, =CH), 6.93–6.99 m (1H, H_{arom}), 7.18–7.25 m (2H, H_{arom}), 7.44–7.49 m (2H, H_{arom}), 8.65 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.8, 13.1, 21.1, 21.8, 24.4, 28.4, 92.0, 106.3, 114.7, 118.7, 121.3, 122.3, 127.6, 139.3, 140.0, 147.5, 150.6, 153.3, 154.3. Found, %: C 73.50; H 6.20; N 20.33. $C_{21}H_{21}N_5$. Calculated, %: C 73.44; H 6.16; N 20.39.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(2-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4b). Yield 586.2 mg (82%), mp 164–165°C. IR spectrum, ν, cm^{-1}: 3387 (NH), 3132 (C–H), 2208 (CN), 1625 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.66–1.75 m (2H, 7-H), 1.82–1.91 m (2H, 6-H), 1.95 d (3H, CH_3, J = 0.6 Hz), 2.15 s (3H, CH_3), 2.23 br.s (3H, CH_3), 2.60 t (2H, 8-H, J = 6.3 Hz), 2.94 t (2H, 5-H, J = 6.3 Hz), 5.77 s (1H, 4-H), 7.02–7.18 m (3H, H_{arom}), 7.29 d.d (1H, H_{arom}, J = 7.8, 1.5 Hz), 8.17 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.6, 13.0, 17.7, 21.2, 21.9, 24.5, 28.4, 90.5, 106.3, 114.9, 117.3, 124.8, 125.5, 126.1, 129.7, 133.4, 137.4, 140.2, 147.3, 150.9, 154.0, 154.6. Found, %: C 73.84; H 6.52; N 19.52. $C_{22}H_{23}N_5$. Calculated, %: C 73.92; H 6.49; N 19.59.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(3-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4c). Yield 600.5 mg (84%), mp 182–183°C. IR spectrum, ν, cm^{-1}: 3392 (NH), 3138 (C–H), 2212 (CN), 1626 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.68–1.76 m (2H, 7-H), 1.83–1.92 m (2H, 6-H), 2.19 s (3H, CH_3), 2.21 s (3H, CH_3), 2.30 s (3H, CH_3), 2.57–2.64 m (2H, 8-H), 2.90–2.97 m (2H, 5-H), 5.86 s (1H, 4′-H), 6.78 d (1H, H_{arom}, J = 7.5 Hz), 7.06–7.12 m (2H, H_{arom}), 7.27 d.d (1H, H_{arom}, J = 2.6, 1.9 Hz), 8.54 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.7, 13.1, 20.9, 21.1, 21.8, 24.5, 28.4, 92.0, 106.2, 106.3, 114.7, 118.5, 118.6, 121.9, 123.2, 127.5, 136.8, 139.2, 139.9, 147.5, 150.7, 153.3, 154.3. Found, %: C 73.87; H 6.45; N 19.67. $C_{22}H_{23}N_5$. Calculated, %: C 73.92; H 6.49; N 19.59.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(4-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4d). Yield 629.1 mg (88%), mp 229–230°C. IR spectrum, ν, cm^{-1}: 3403 (NH), 3128 (C–H), 2209 (CN), 1627 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.67–1.75 m (2H, 7-H), 1.83–1.91 m (2H, 6-H), 2.16 d (3H, CH_3, J = 0.6 Hz), 2.18 s (3H, CH_3), 2.30 s (3H, CH_3), 2.56–2.61 m (2H, 8-H), 2.90–2.96 m (2H, 5-H), 5.85 br.s (1H, 4′-H), 6.99–7.04 m (2H, H_{arom}), 7.30–7.35 m (2H, H_{arom}), 8.56 m (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.8, 13.1, 20.3, 21.2, 21.8, 24.4, 28.4, 91.6, 106.2, 114.8, 118.3, 121.7, 128.2, 131.4, 136.6, 139.9, 147.5, 150.7, 153.5, 154.2. Found, %: C 73.98; H 6.46; N 19.55. $C_{22}H_{23}N_5$. Calculated, %: C 73.92; H 6.49; N 19.59.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(2-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4e). Yield 619.9 mg (83%), mp 190–191°C. IR spectrum, ν, cm^{-1}: 3399 (NH), 3126 (C–H), 2211 (CN), 1625 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.68–1.77 m (2H, 7-H), 1.84–1.92 m (2H, 6-H), 2.23 s (3H, CH_3), 2.24 s (3H, CH_3), 2.61 t (2H, 8-H, J = 6.2 Hz), 2.96 t (2H, 5-H, J = 6.3 Hz), 3.94 s (3H, OCH_3), 5.91 br.s (1H, 4′-H), 6.83–7.00 m (3H, H_{arom}), 7.85 s (1H, NH), 8.06 d.d (1H, H_{arom}, J = 8.1, 1.4 Hz). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.6, 13.1, 21.0, 21.7, 24.3, 28.3, 55.3, 92.1, 104.8, 106.4, 109.6, 114.4, 118.9, 119.6, 120.0, 122.4, 128.0, 139.9, 147.7, 148.5, 150.6, 152.6, 154.0. Found, %: C 70.82; H 6.24; N 18.67. $C_{22}H_{23}N_5O$. Calculated, %: C 70.76; H 6.21; N 18.75

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(3-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4f). Yield 642.3 mg (86%), mp 170–171°C. IR spectrum, ν, cm^{-1}: 3406 (NH), 3129 (C–H), 2210 (CN), 1628 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.68–1.76 m (2H, 7-H), 1.84–

1.91 m (2H, 6-H), 2.19 s (3H, CH_3), 2.21 s (3H, CH_3), 2.57–2.62 m (2H, 8-H), 2.91–2.97 m (2H, 5-H), 3.77 s (3H, OCH_3), 5.87 s (1H, 4′-H), 6.48–6.53 m (1H, H_{arom}), 7.07–7.16 m (3H, H_{arom}), 8.67 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.8, 13.1, 21.1, 21.8, 24.4, 28.4, 54.3, 92.3, 106.2, 106.7, 107.9, 113.2, 114.6, 118.9, 128.2, 139.9, 140.5, 147.6, 150.6, 153.1, 154.4, 159.1. Found, %: C 70.69; H 6.16; N 18.70. $C_{22}H_{23}N_5O$. Calculated, %: C 70.76; H 6.21; N 18.75.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(4-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4g). Yield 619.9 mg (83%), mp 190–191°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 3128 (C–H), 2208 (CN), 1624 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.66–1.74 m (2H, 7-H), 1.82–1.92 m (2H, 6-H), 2.13 d (3H, CH_3, J = 0.7 Hz), 2.18 s (3H, CH_3), 2.55–2.60 m (2H, 8-H), 2.90–2.95 m (2H, 5-H), 3.75 s (3H, OCH_3), 5.83 br.s (1H, 4′-H), 6.74–6.79 m (2H, H_{arom}), 7.29–7.34 m (2H, H_{arom}), 8.46 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.8, 13.0, 21.2, 21.9, 24.4, 28.3, 54.5, 91.0, 106.1, 112.9, 114.8, 117.8, 123.8, 132.0, 140.0, 147.4, 150.7, 153.9, 154.1, 155.3. Found, %: C 70.84; H 6.18; N 18.82. $C_{22}H_{23}N_5O$. Calculated, %: C 70.76; H 6.21; N 18.75.

3-(4-Chloroanilino)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4h). Yield 642.4 mg (85%), mp 210–211°C. IR spectrum, ν, cm^{-1}: 3395 (NH), 3118 (C–H), 2214 (CN), 1628 (C=C). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.67–1.77 m (2H, 7-H), 1.83-1.92 m (2H, 6-H), 2.17 br.s (3H, CH_3), 2.19 s (3H, CH_3), 2.57–2.63 m (2H, 8-H), 2.91–2.97 m (2H, 5-H), 5.87 s (1H, 4′-H), 7.15–7.21 m (2H, H_{arom}), 7.47–7.53 m (2H, H_{arom}), 8.90 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 11.8, 13.1, 21.1, 21.7, 24.4, 28.4, 92.3, 106.3, 114.6, 119.2, 122.5, 126.5, 127.5, 138.2, 139.9, 147.6, 150.5, 152.9, 154.5. Found, %: C 66.87; H 5.30; N 18.47. $C_{21}H_{20}ClN_5$. Calculated, %: C 66.75; H 5.33; N 18.53.

Compounds 5a–5h (*general procedure*). A solution of 1.4 g (20 mmol) of sodium nitrite in 10 mL of water was added dropwise with stirring to a mixture of 10 mmol of compound **2a**–**2h** and 50 mL of glacial acetic acid, cooled to 0°C. The mixture was stirred for 12 h at room temperature, and the precipitate was filtered off, washed with water, and recrystallized from ethanol–methylene chloride (1:3).

3-Anilino-1-azido-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5a). Yield 2.323 g (80%), mp 189–190°C. IR spectrum, ν, cm^{-1}: 3324 (NH), 2210 (CN), 2136 (N_3), 1615 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.73–1.86 m (4H, 6-H, 7-H), 2.42–2.48 m (2H, 8-H), 2.80–2.86 m (2H, 5-H), 6.92 br.s (1H, NH), 7.07–7.12 m (1H, H_{arom}), 7.31–7.39 m (2H, H_{arom}), 7.60–7.65 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.7, 22.1, 22.9, 28.6, 88.6, 114.2, 116.2, 120.2, 123.4, 128.9, 138.8, 153.6, 154.0, 155.4. Found, %: C 66.27; H 4.83; N 28.88. $C_{16}H_{16}N_6$. Calculated, %: C 66.19; H 4.86; N 28.95

1-Azido-3-(2-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5b). Yield 2.709 g (89%), mp 146–147°C. IR spectrum, ν, cm^{-1}: 3186 (NH), 2205 (CN), 2138 (N_3), 1624 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.87 m (4H, 6-H, 7-H), 2.36 s (3H, CH_3), 2.41–2.48 m (2H, 8-H), 2.80–2.88 m (2H, 5-H), 6.78 br.s (1H, NH), 7.02–7.09 m (1H, H_{arom}), 7.18–7.26 m (2H, H_{arom}), 7.95–8.00 m (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.1, 21.9, 22.3, 23.0, 28.7, 88.6, 113.9, 116.2, 122.6, 124.4, 126.6, 129.1, 130.6, 137.0, 153.4, 154.6, 155.4. Found, %: C 67.17; H 5.35; N 27.52. $C_{17}H_{16}N_6$. Calculated, %: C 67.09; H 5.30; N 27.61.

1-Azido-3-(3-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5c). Yield 2.648 g (87%), mp 157–158°C. IR spectrum, ν, cm^{-1}: 3019 (NH), 2208 (CN), 2132 (N_3), 1634 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.87 m (4H, 6-H, 7-H), 2.38 s (3H, CH_3), 2.43–2.48 m (2H, 8-H), 2.81–2.87 m (2H, 5-H), 6.83 br.s (1H, NH), 6.90 br.d (1H, H_{arom}, J = 8.1 Hz), 6.90 d.d (1H, H_{arom}, J = 8.1, 7.9 Hz), 7.33 br.d (1H, H_{arom}, J = 7.9 Hz), 7.60 br.s (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9, 21.2, 21.5, 22.2, 27.8, 88.7, 112.7, 114.9, 117.6, 121.1, 122.8, 127.3, 136.7, 138.9, 153.0, 153.6, 153.8. Found, %: C 67.02; H 5.26; N 27.67. $C_{17}H_{16}N_6$. Calculated, %: C 67.09; H 5.30; N 27.61.

1-Azido-3-(4-methylanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5d). Yield 2.739 mg (90%), mp 175–176°C. IR spectrum, ν, cm^{-1}: 3341 (NH), 2209 (CN), 2137 (N_3), 1614 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.85 m (4H, 6-H, 7-H), 2.35 s (3H, CH_3), 2.41–2.47 m (2H, 8-H), 2.80–2.86 m (2H, 5-H), 6.86 br.s (1H, NH), 7.12–7.16 m (2H, H_{arom}), 7.46–7.51 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9, 21.8, 22.2, 23.0, 28.6, 88.4, 96.3, 113.4, 116.1, 120.5, 129.4, 133.0, 136.3, 153.5, 154.2, 155.4. Found, %: C 67.15; H 5.34;

N 27.53. $C_{17}H_{16}N_6$. Calculated, %: C 67.09; H 5.30; N 27.61.

1-Azido-3-(2-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5e). Yield 2.755 g (86%), mp 173–174°C. IR spectrum, ν, cm^{-1}: 3393 (NH), 2201 (CN), 2134 (N_3), 1612 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.87 m (4H, 6-H, 7-H), 2.43–2.49 m (2H, 8-H), 2.81–2.89 m (2H, 5-H), 3.97 s (3H, OCH_3), 6.89–7.03 m (3H, H_{arom}), 7.79 br.s (1H, NH), 8.46–8.51 m (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.8, 22.2, 23.0, 28.6, 56.0, 89.5, 110.0, 113.8, 115.9, 119.2, 120.8, 122.5, 128.9, 148.2, 153.5, 153.9, 155.4. Found, %: C 63.68; H 5.08; N 26.16. $C_{17}H_{16}N_6O$. Calculated, %: C 63.74; H 5.03; N 26.23.

1-Azido-3-(3-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5f). Yield 2.595 g (81%), mp 166–167°C. IR spectrum, ν, cm^{-1}: 3363 (NH), 2208 (CN), 2129 (N_3), 1618 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.85 m (4H, 6-H, 7-H), 2.42–2.48 m (2H, 8-H), 2.79–2.85 m (2H, 5-H), 3.85 s (3H, OCH_3), 6.63 d.d.d (1H, H_{arom}, J = 8.1, 2.5, 0.7 Hz), 6.93 br.s (1H, NH), 7.05 d.d.d (1H, H_{arom}, J = 8.1, 2.1, 0.7 Hz), 7.21 t (1H, H_{arom}, J = 8.1 Hz), 7.37 d.d (1H, H_{arom}, J = 2.5, 2.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.8, 22.2, 23.0, 28.7, 55.4, 89.0, 105.6, 109.6, 112.3, 114.3, 116.0, 129.6, 140.1, 153.6, 154.0, 155.3, 160.4. Found, %: C 63.80; H 4.97; N 26.32. $C_{17}H_{16}N_6O$. Calculated, %: C 63.74; H 5.03; N 26.23.

1-Azido-3-(4-methoxyanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5g). Yield 2.851 g (89%), mp 151–152°C. IR spectrum, ν, cm^{-1}: 3385 (NH), 2205 (CN), 2131 (N_3), 1610 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.73–1.85 m (4H, 6-H, 7-H), 2.40–2.46 m (2H, 8-H), 2.79–2.85 m (2H, 5-H), 3.82 s (3H, OCH_3), 6.78 br.s (1H, NH), 6.85–6.91 m (2H, H_{arom}), 7.45–7.50 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.8, 23.0, 28.7, 55.6, 89.0, 111.4, 113.1, 124.5, 127.3, 130.0, 132.6, 148.8, 153.7, 154.2, 155.4. Found, %: C 63.65; H 5.11; N 26.13. $C_{17}H_{16}N_6O$. Calculated, %: C 63.74; H 5.03; N 26.23.

1-Azido-3-(4-chloroanilino)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (5h). Yield 2.988 g (92%), mp 195–196°C. IR spectrum, ν, cm^{-1}: 3321 (NH), 2208 (CN), 2134 (N_3), 1606 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.73–1.87 m (4H, 6-H, 7-H), 2.41–2.48 m (2H, 8-H), 2.81–2.87 m (2H, 5-H), 6.90 br.s (1H, NH), 7.28–7.34 m (2H, H_{arom}), 7.55–7.60 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.8, 22.2, 23.0, 28.7, 88.9, 114.6, 115.9, 121.5, 128.6, 129.0, 137.4, 153.7, 153.8, 155.4. Found, %: C 59.26; H 4.29; N 25.79. $C_{16}H_{13}ClN_6$. Calculated, %: C 59.17; H 4.03; N 25.88.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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