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Synthesis of partially hydrogenated isoquinoline derivatives by condensation of 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones with malononitrile and its dimer and a study of their alkylation

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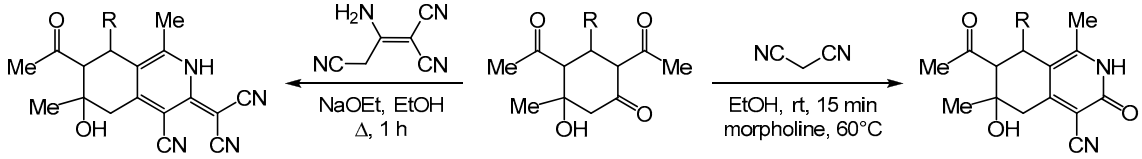


New derivatives of partially hydrogenated isoquinolines were obtained by condensation of 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones with malononitrile and its dimer, 2-amino-1,1,3-tricyano-1-propene, and alkylation reactions of the obtained compounds were studied.

Keywords: 2-amino-1,1,3-tricyano-1-propene, 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones, malononitrile, alkylation, partially hydrogenated isoquinolines, condensation.

β-Cycloketols **1** have shown antimicrobial activity[1] and are available as reagents for the synthesis of biologically active heterocyclic compounds.[2] The reactions of these compounds with hydrazine and hydroxylamine have received most attention,[3] while several studies report also their condensation reactions with CH acids – cyanoacetamide,[4] cyanothioacetamide,[4,5] cyanoselenoacetamide[6], and 1-phenyl-1*H*-pyrazol-5*H*-one.[7]

In order to further the understanding of reactivity of 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones **1a**–**g**,[5–7] in the current work, we studied their condensation with malononitrile (**2**) and its dimer, 2-amino-1,1,3-tricyano-1-propene (**3**) (Scheme 1). These reactions occurred at 60°C in anhydrous ethanol in the presence of morpholine and produced 7-acetyl-8-aryl(hetaryl)-6-hydroxy-1,6-dimethyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles **4a**–**e** (method I) or 2-[7-acetyl-8-aryl (hetaryl)-4-cyano-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]malononitriles **5a**–**c**,**f**,**g**, respectively.

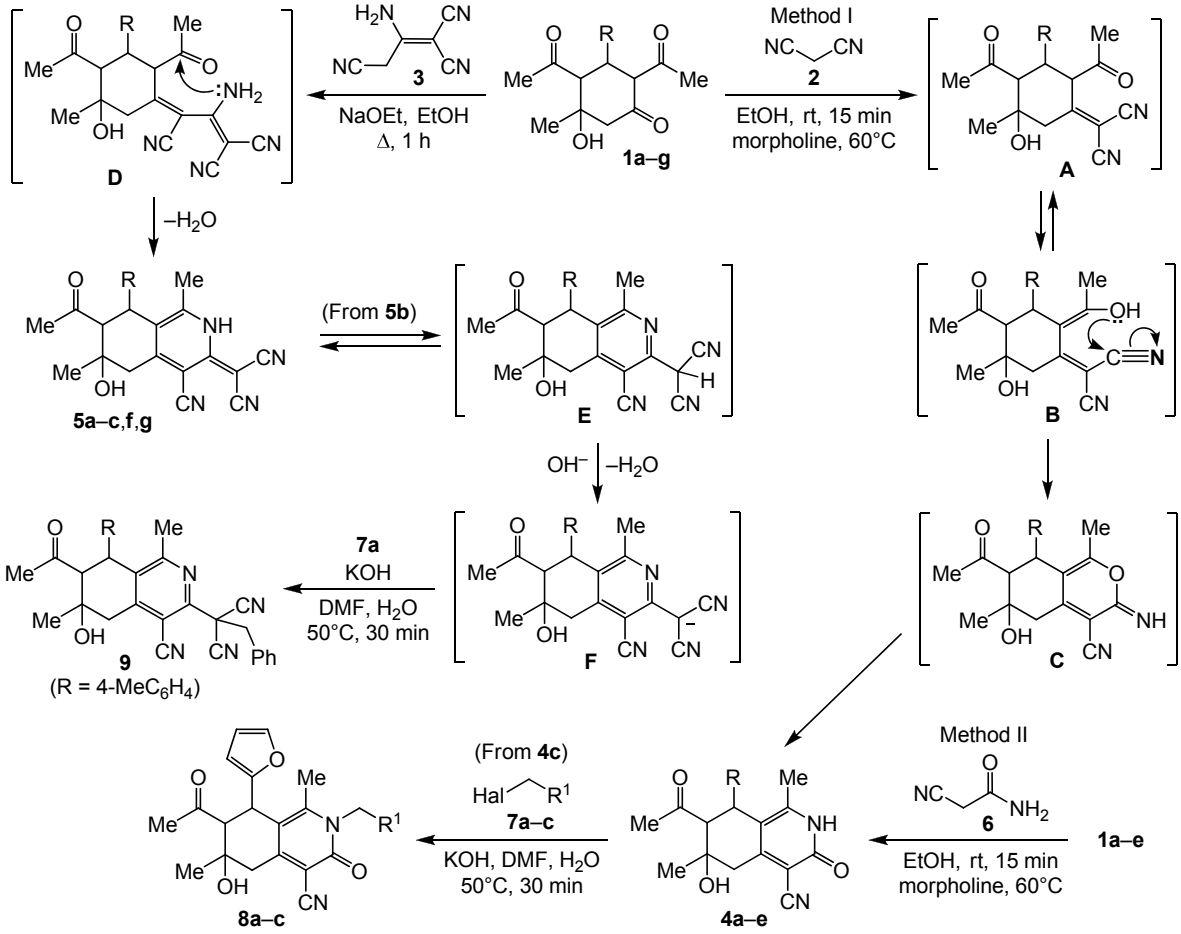
The likely mechanism for the formation of the indicated partially hydrogenated isoquinolines **4a**–**e** was the following. At first, a Knoevenagel condensation gave the alkene **A** that could enolize in basic medium to the intermediate **B**, with further intramolecular cyclization to the iminopyran **C**. The intermediate **B** underwent a Dimroth recyclization[8] to the final product **4**. Compounds **4a**–**e** were also obtained by counter synthesis through condensation of cycloketols **1a**–**e** with cyanoacetamide (**6**) in the presence of morpholine (method II).[4] We should note that compounds **4a**,**b** were previously prepared by condensation of the substituted cyclohexanones **1a**,**b** with cyanoacetamide (**6**) upon heating in ethanol in the presence of sodium methoxide.[4]

Compounds **5a**–**c**,**f**,**g** were apparently formed by a mechanism similar to the scheme given for substituted isoquinolinones **4a**–**e**: the Knoevenagel alkene **D** underwent intramolecular cyclization to a pyridine system, resulting in 3-dicyanomethylene-substituted partially hydrogenated isoquinoline derivatives **5a**–**c**,**f**,**g**.

The structures of the synthesized compounds **4a**–**e**, **5a**–**c**,**f**,**g** were confirmed by spectral data. The IR spectra contained characteristic stretching vibration bands of the conjugated cyano group and carbonyl group at 2157–2236 and 1687–1715 cm^{-1}, respectively. All carbon atoms in these molecules gave the expected ^{13}C NMR signals in the appropriate regions. All the substituents and the cyclohexane fragment gave ^{1}H NMR signals with characteristic splitting patterns.[4,5]

The presence of several reaction centers in the partially hydrogenated isoquinoline systems **4**, **5,** namely, NH, OH, and C=O groups, allowed to perform reactions with alkylating agents **7a**–**c**. Alkylation of substituted 3-cyano-1,2-dihydropyridin-2-ones usually leads to a mixture of *N*- and *O*-alkyl derivatives.[9,10] In the current study, we showed that reactions of isoquinolinone **4c** with alkyl halides **7a**–**c** in DMF at 50°C in the presence of 10%

Scheme 1



1, **4**, **5 a** R = Ph, **b** R = 4-MeC_6H_4, **c** R = 2-Fur, **d** R = 5-methylfuran-2-yl, **e** R = 3-Py, **f** R = 4-(*i*-Pr)C_6H_4, **g** R = 3-$MeOC_6H_4$;
7 a Hal = Cl, **b** Hal = I, **c** Hal = Br; **7**, **8 a** R^1 = Ph, **b** R^1 = H, **c** R^1 = –CH=CH_2

aqueous KOH gave the respective *N*-alkyl derivatives **8a**–**c**. The IR spectra of the synthesized compounds **8a**–**c** were found to be quite informative for structural characterization, thus proving the regioselectivity of the studied alkylation reaction. For example, the IR spectra of compounds **8a**–**c** contained not only the absorption bands of functional groups, but also showed the characteristic stretching vibrations of the isoquinoline ring amide moiety at 1621–1634 cm^{-1}.[11]

Alkylation of the partially hydrogenated isoquinoline **5b** with benzyl chloride (**7a**) under conditions analogous to those described above also occurred regioselectively, but at the C-2 atom of malononitrile fragment. The reaction apparently involved the formation of prototropic tautomer **E** and the respective carbanion **F**, and led to the corresponding product, 2-[7-acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-(4-methylphenyl)-5,6,7,8-tetrahydroisoquinolin-3-yl]-2-benzylmalononitrile (**9**). We should note that the same regioselectivity of alkylation was also observed for 1-alkyl(aryl)-3-dicyanomethylene-4-cyano-substituted carbo[*c*]annelated pyridines,[12] which are isostructural analogs of compound **5**. This could probably be explained by the rapid exchange of NH protons in the isoquinoline ring. The X-ray structural analysis data obtained for a related compound, 3-cyano-2-dicyanomethylene-5,6-dimethyl-1,2-dihydropyridine, indicated a planar structure with aromatic properties,[13] which could contribute to the NH acidity.

The structure of compound **9** was confirmed by its spectral characteristics, especially the ^{13}C NMR spectrum, which contained 10 aliphatic carbon signals in the appropriate regions. In the case of *N*-alkylation product, the aliphatic region should contain nine signals. We should also note the restricted rotation of the benzyl fragment in this molecule, apparently due to steric obstacles, which was observed as nonequivalence of methylene group protons and, as a consequence, splitting of these signals in two doublets with ^2J = 14.0 Hz. The IR spectrum of isoquinoline **9** featured characteristic absorption bands due to all functional groups present in the molecule, except the nonconjugated nitrile groups, which may be unobservable according to the literature data.[14]

Mass spectra of the majority of synthesized compounds contained molecular ion peaks with *m*/*z* values in accordance with the "nitrogen rule".[15]

Thus, condensation of 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones with malononitrile or its dimer, 2-amino-1,1,3-tricyano-1-propene, was used to synthesize 7-acetyl-8-aryl(hetaryl)-6-hydroxy-1,6-dimethyl-

3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles and 7-acetyl-2-(8-aryl(hetaryl)-4-cyano-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene)malononitriles, respectively. Alkylation of substituted 3-oxoisoquinolines occurred at nitrogen atom, while (isoquinolin-3(2*H*)-ylidene)malononitriles were alkylated at the C-2 atom of the malononitrile fragment.

Experimental

IR spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on an MKh-1321 mass spectrometer (70 eV) with direct introduction of sample into the ion source. Elemental analysis was performed on a Eurovector EA-3000 instrument. Melting points were determined on a Kofler hot bench. The reaction progress and the purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates, eluent was 3:5 acetone–hexane, visualization with iodine vapor and under UV light.

2,4-Diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones 1a–g were obtained according to a published procedure.[3]

Preparation of Compounds 4a–e (General Method).

Method I. A suspension of substituted cyclohexanone **1a–e** (6 mmol) in anhydrous EtOH (20 ml) was treated by addition of malononitrile (**2**) (0.40 g, 6 mmol). The reaction mixture was stirred for 15 min at room temperature, then morpholine (0.52 ml, 6 mmol) was added; the stirred reaction mixture was heated to 60°C, then heating was abruptly stopped and the mixture was cooled to 15°C over 1 h. The precipitate formed was filtered off after 24 h, washed with EtOH, hexane, and recrystallized from EtOH.

Method II. The procedure was analogous to method I, except that cyanoacetamide (**6**) (0.50 g, 6 mmol) was used instead of malononitrile (**2**).

7-Acetyl-6-hydroxy-1,6-dimethyl-3-oxo-8-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4a). Yield 1.80 g (89%, method I), 1.85 g (91%, method II), white powder, mp 235–237°C (mp 247–264°C[4]). Mass spectrum, *m*/*z* (I_{rel}, %): 336 $[M]^+$ (1), 318 $[M–H_2O]^+$ (2), 275 $[M–H_2O–CH_3CO]^+$ (100), 261 (11), 199 (19), 77 $[C_6H_5]^+$ (12), 43 $[CH_3CO]^+$ (89).

7-Acetyl-6-hydroxy-1,6-dimethyl-8-(4-methylphenyl)-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4b). Yield 1.70 g (81%, method I), 1.95 g (93%, method II), white powder, mp 255–257°C (mp 267–268°C[4]). Mass spectrum, *m*/*z* (I_{rel}, %): 349 $[M–H]^+$ (1), 332 $[M–H_2O]^+$ (1), 312 (10), 289 $[M–H_2O–CH_3CO]^+$ (100), 276 (15), 199 (9), 105 (6), 91 $[C_6H_5CH_2]^+$ (6), 44 $[CH_3COH]^+$ (31), 30 (28).

7-Acetyl-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4c). Yield 1.70 g (87%, method I), 1.85 g (94%, method II), white powder, fluorescent under UV light, mp 235–237°C. IR spectrum, ν, cm^{-1}: 3364 (OH), 3005 (NH), 2221 (CN), 1715 (C=O), 1655 (NHCO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, CH_3); 1.96 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.80 (1H, d, *J* = 16.5, 5-CH_A); 2.93–3.02 (2H, m, 5-CH_B, 7-CH); 4.50 (1H, d, *J* = 4.6, 8-CH); 5.01 (1H, br. s, OH); 6.08 (1H, s, H-3 Fur); 6.33 (1H, s, H-4 Fur); 7.52 (1H, s, H-5 Fur); 12.41 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 17.1; 28.0; 30.7; 34.9; 43.4; 61.8; 67.9; 98.8; 106.4; 110.4; 112.5; 115.9; 141.9; 150.4; 155.2; 158.6; 159.8; 208.4. Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M]^+$ (1), 308 $[M–H_2O]^+$ (2), 283 $[M–CH_3CO]^+$ (3), 265 $[M–H_2O–CH_3CO]^+$ (100), 251 (11), 237 (8), 223 (53), 43 $[CH_3CO]^+$ (72). Found, %: C66.16; H5.41; N 8.49. $C_{18}H_{18}N_2O_4$. Calculated, %: C66.25; H5.56; N 8.58.

7-Acetyl-6-hydroxy-1,6-dimethyl-8-(5-methylfuran-2-yl)-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4d). Yield 1.73 g (85%, method I), 1.80 g (88%, method II), white powder, mp 237–240°C. IR spectrum, ν, cm^{-1}: 3426 (OH), 3248 (NH), 2236 (CN), 1695 (C=O), 1671 (NHCO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, s, CH_3); 2.00 (3H, s, CH_3); 2.16 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.79 (1H, d, *J* = 15.0, 5-CH_A); 2.84–3.02 (2H, m, 5-CH_B, 7-CH); 4.41 (1H, d, *J* = 4.5, 8-CH); 4.98 (1H, br. s, OH); 5.91 (2H, d, *J* = 2.1, H-3,4 Fur). The NH proton signal was not observed apparently due to fast deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 11.9; 16.1; 26.9; 29.5; 33.7; 42.1; 60.4; 66.8; 97.6; 105.0; 105.8; 111.4; 114.7; 149.2 (2C); 152.0; 157.4; 158.6; 207.3. Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ was absent, 322 $[M–H_2O]^+$ (3), 279 $[M–H_2O–CH_3CO]^+$ (91), 265 (10), 237 (14), 198 (4), 169 (4), 77 (5), 44 $[CH_3COH]^+$ (100). Found, %: C 66.93; H 5.85; N 8.15. $C_{19}H_{20}N_2O_4$. Calculated, %: C 67.05; H 5.92; N 8.23.

7-Acetyl-6-hydroxy-1,6-dimethyl-3-oxo-8-(pyridin-3-yl)-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4e). Yield 1.72 g (85%, method I), 1.82 g (90%, method II), white powder, mp 257–259°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 3270 (NH), 2220 (CN), 1695 (C=O), 1665 (NHCO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, s, CH_3); 1.76 (3H, s, CH_3); 2.07 (3H, s, CH_3); 2.87 (1H, d, *J* = 10.1) and 4.35 (1H, d, *J* = 10.1, 5-CH_2); 3.01 (1H, s, 7-CH); 3.75 (1H, s, 8-CH); 4.74 (1H, br. s, OH); 7.21 (1H, t, *J* = 7.7, H-5 Py); 7.43 (1H, d, *J* = 7.6, H-4 Py); 8.27 (1H, s, H-2 Py); 8.35 (1H, d, *J* = 7.4, H-6 Py); 12.31 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 19.2; 28.5; 31.9; 44.9; 66.4; 68.5; 99.9; 115.4; 116.7; 116.8; 124.3; 136.0; 140.7; 148.4; 150.1; 151.0; 151.1; 160.6; 209.5. Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ was absent, 319 $[M–H_2O]^+$ (4), 294 $[M–CH_3CO]^+$ (8), 276 $[M–H_2O–CH_3CO]^+$ (100), 236 (4), 199 (14), 104 (3), 79 $[C_6H_5+2H]^+$ (9), 43 $[CH_3CO]^+$ (48), 44 $[CH_3COH]^+$ (48), 30 (31). Found, %: C 67.48; H 5.52; N 12.32. $C_{19}H_{19}N_3O_3$. Calculated, %: C 67.64; H 5.68; N 12.45.

Preparation of compounds 5a–c,f,g (General Method). A suspension of cyclohexanone **1a–c,f,g** (6 mmol) in anhydrous EtOH (30 ml) was treated by addition of malononitrile dimer **3** (0.80 g, 6 mmol) and sodium ethoxide solution prepared from sodium metal (0.14 g, 6 mmol) and anhydrous EtOH (5 ml). The reaction mixture was refluxed for 1 h in a flask with a reflux condenser and left at room temperature. After 48 h the reaction mixture was diluted with 10% HCl to pH 7, the precipitate formed

was filtered off, washed with water, then with EtOH, hexane, and recrystallized from *n*-BuOH.

2-[7-Acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-phenyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]malononitrile (5a). Yield 1.57 g (68%), yellow crystals, fluorescent under UV light, mp 285–288°C. IR spectrum, ν, cm^{-1}: 3411 (OH), 2922 (NH), 2210, 2191, 2157 (CN), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, s, CH_3); 1.74 (3H, s, CH_3); 2.01 (3H, s, CH_3); 2.72–2.84 (2H, m, 5-CH_A, 7-CH); the signal of second 5-CH_2 proton overlapped with residual water signal; 4.30 (1H, d, *J* = 10.9, 8-CH); 4.47 (1H, br. s, OH); 6.96 (2H, d, *J* = 7.4, H Ph); 7.13 (1H, t, *J* = 7.3, H Ph); 7.21 (2H, t, *J* = 7.3, HPh). The signal of NH proton was not observed, apparently due to fast deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 384 $[M]^+$ (3), 367 $[M+H–H_2O]^+$ (63), 366 $[M–H_2O]^+$ (13), 352 $[M+H–H_2O–CH_3]^+$ (95), 289 $[M–H_2O–C_6H_5]^+$ (100), 274 $[M–H_2O–C_6H_5–CH_3]^+$ (6), 183 (10), 176 (13), 168 (11), 77 $[C_6H_5]^+$ (3), 60 (30), 44 $[CH_3COH]^+$ (47), 43 $[CH_3CO]^+$ (7). Found, %: C 71.66; H 5.11; N 14.45. $C_{23}H_{20}N_4O_2$. Calculated, %: C 71.86; H 5.24; N 14.57.

2-[7-Acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-(4-methylphenyl)-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]-malononitrile (5b). Yield 1.86 g (78%), orange powder, mp 246–247°C. IR spectrum, ν, cm^{-1}: 3437 (OH), 2923 (NH), 2222, 2203, 2182 (CN), 1697 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, s, CH_3); 2.03 (3H, s, CH_3); 2.04 (3H, s, CH_3); 2.29 (3H, s, CH_3); 2.81–2.98 (2H, m, 5-CH_A, 7-CH); 3.15 (1H, d, *J*=19.4, 5-CH_B); 4.36 (1H, d, *J* = 10.2, 8-CH); 6.93 (2H, d, *J* = 7.8, H Ar); 7.04 (2H, d, *J* = 7.8, H Ar). The NH and OH proton signals were not observed apparently due to fast deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 398 $[M]^+$ (2), 380 $[M–H_2O]^+$ (2), 337 $[M–H_2O–CH_3CO]^+$ (84), 323 $[M+H–H_2O–CH_3CO]^+$ (20), 247 $[M+H–H_2O–CH_3CO–C_6H_4CH_3]^+$ (21), 161 (8), 91 $[C_6H_4CH_3]^+$ (10), 44 $[CH_3COH]^+$ (100), 30 (25). Found, %: C 72.20; H 5.43; N 13.92. $C_{24}H_{22}N_4O_2$. Calculated, %: C 72.34; H 5.57; N 14.06.

2-[7-Acetyl-4-cyano-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]-malononitrile (5c). Yield 1.80 g (80%), yellow powder, fluorescent under UV light, mp 228–230°C. IR spectrum, ν, cm^{-1}: 3382 (OH), 2924 (NH), 2224, 2202, 2176 (CN), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, s, CH_3); 2.19 (3H, s, CH_3); 2.27 (3H, s, CH_3); 2.86 (1H, d, *J* = 14.0) and 2.99 (1H, d, *J* = 14.0, 5-CH_2); 3.14 (1H, d, *J* = 7.8, 7-CH); 4.60 (1H, d, *J* = 7.8, 8-CH); 6.09 (1H, s, H-3 Fur); 6.30 (1H, s, H-4 Fur); 7.41 (1H, d, *J* = 1.2, H-5 Fur). The NH and OH proton signals were not observed apparently due to fast deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 375 $[M+H]^+$ (100). Found, %: C 67.23; H 4.76; N 14.80. $C_{21}H_{18}N_4O_3$. Calculated, %: C 67.37; H 4.85; N 14.96.

2-[7-Acetyl-4-cyano-6-hydroxy-8-(4-isopropylphenyl)-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]malononitrile (5f). Yield 1.94 g (76%), orange powder, mp 232–234°C. IR spectrum, ν, cm^{-1}: 3473 (OH), 2924 (NH), 2218, 2201, 2177 (CN), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (6H, d, *J*=6.9, $CH(C\underline{H}_3)_2$); 1.28 (3H, s, CH_3); 2.03 (3H, s, CH_3); 2.04 (3H, s, CH_3); 2.79–2.85 (1H, m, $C\underline{H}Me_2$); 2.86–2.99 (2H, m, 5-CH_A, 7-CH); 3.11 (1H, d, *J* = 17.4, 5-CH_B); 4.36 (1H, d, *J* = 10.0, 8-CH); 6.94 (2H, d, *J* = 7.8, H Ar); 7.08 (2H, d, *J* = 7.8, H Ar). The NH and OH proton signals were not observed apparently due to fast deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ was absent, 408 $[M–H_2O]^+$ (2), 365 $[M–CH_3CO]^+$ (57), 351 $[M+H–H_2O–CH_3CO–CH_3]^+$ (14), 247 (16), 44 $[CH_3COH]^+$ (100). Found, %: C 73.12; H 6.00; N 13.04. $C_{26}H_{26}N_4O_2$. Calculated, %: C 73.22; H 6.14; N 13.14.

2-[7-Acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-(3-methoxyphenyl)-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-ylidene]malononitrile (5g). Yield 2.01 g (81%), yellow powder, mp 235–237°C. IR spectrum, ν, cm^{-1}: 3448 (OH), 2920 (NH), 2225, 2199, 2173 (CN), 1692 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, s, CH_3); 2.04 (3H, s, CH_3); 2.06 (3H, s, CH_3); 2.83–2.98 (2H, m, 5-CH_A, 7-CH); 3.13 (1H, d, *J* = 17.6, 5-CH_B); 3.73 (3H, s, OCH_3); 4.37 (1H, d, *J* = 10.3, 8-CH); 5.55–6.61 (2H, m, H Ar); 6.70 (1H, d, *J* = 9.4, H Ar); 7.15 (1H, t, *J* = 8.1, HAr). The NH and OH proton signals were not observed apparently due to fast deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 414 $[M]^+$ (3), 396 $[M–H_2O]^+$ (3), 339 $[M+H–H_2O–CH_3CO–CH_3]^+$ (9), 247 (24), 161 (45), 44 $[CH_3COH]^+$ (100), 30 (70). Found, %: C 69.41; H 5.20; N 13.43. $C_{24}H_{22}N_4O_3$. Calculated, %: C 69.55; H 5.35; N.52.

Preparation of Compounds 8a–c, **9** (General Method). A stirred solution of substituted isoquinoline **4c**, **5b** (2 mmol) in DMF (10 ml) was treated by adding 10% aqueous KOH solution (1.12 ml, 2 mmol), followed by alkylating agent **7a**–**c** (2 mmol). The reaction mixture was stirred and slowly heated for 30 min, until 50°C temperature was reached, then diluted with equal amount of H_2O and left at room temperature. The precipitate formed was filtered off after 48 h, washed with water, EtOH, hexane, and recrystallized from EtOH (compounds **8a**–**c**) or *n*-BuOH (compound **9**).

7-Acetyl-2-benzyl-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (8a). Yield 0.76 g (91%), white powder, mp 118–119°C. IR spectrum, ν, cm^{-1}: 3350 (OH), 2221 (CN), 1703 (C=O), 1634 (N–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.21 (3H, s, CH_3); 2.81–2.95 (2H, m, 5-CH_A, 7-CH); the signal of second 5-CH_2 proton overlapped with residual water signal; 4.54 (1H, d, *J* = 6.8, 8-CH); 4.93 (1H, br. s, OH); 5.40 (2H, s, NCH_2); 5.90 (1H, s, H-3 Fur); 6.24 (1H, s, H-4 Fur); 7.10 (2H, d, *J*= 7.5, HPh); 7.24 (1H, t, *J* = 7.2, H Ph); 7.26–7.41 (3H, m, H-5 Fur, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ was absent, 214 (41), 213 (47), 186 (22), 185 (10), 137 (26), 105 (100), 77 (70), 70 (21), 68 (11), 51 (19), 44 $[CH_3COH]^+$ (8). Found, %: C 71.88; H 5.67; N 6.59. $C_{25}H_{24}N_2O_4$. Calculated, %: C 72.10; H 5.81; N 6.73.

7-Acetyl-8-(furan-2-yl)-6-hydroxy-1,2,6-trimethyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (8b). Yield 0.48 g (71%), white powder, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3354 (OH), 2204 (CN), 1700 (C=O), 1626 (N–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30

(3H, s, CH_3); 2.22 (3H, s, CH_3); 2.24 (3H, s, CH_3); 2.84 (3H, s, CH_3); 3.01–3.28 (2H, m, 5-CH_A, 7-CH); 4.44 (1H, d, J = 4.4, 8-CH); 4.90 (2H, br. s, 5-CH_B, OH); 5.99 (1H, s, H-3 Fur); 6.28 (1H, s, H-4 Fur); 7.41 (1H, s, H-5 Fur). Mass spectrum, m/z (I_{rel}, %): 340 $[M]^+$ (1), 322 $[M–H_2O]^+$ (3), 297 $[M–CH_3CO]^+$ (6), 280 $[M+H–H_2O–CH_3CO]^+$ (21), 279 $[M–H_2O–CH_3CO]^+$ (100), 265 $[M+H–H_2O–CH_3CO–CH_3]^+$ (20), 264 $[M–H_2O–CH_3CO]^+$ (12), 56 (16), 44 $[CH_3COH]^+$ (33), 30 (53). Found, %: C 66.89; H 5.77; N 8.10. $C_{19}H_{20}N_2O_4$. Calculated, %: C 67.05; H 5.92; N 8.23.

7-Acetyl-2-allyl-8-(furan-2-yl)-6-hydroxy-1,6-dimethyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (8c). Yield 0.55 g (82%), white powder, mp 133–135°C. IR spectrum, ν, cm^{-1}: 3324 (OH), 2208 (CN), 1695 (C=O), 1621 (N–C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.29 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.22 (3H, s, CH_3); 2.86–2.99 (2H, m, 5-CH_A, 7-CH); 4.55 (1H, d, J = 17.0, 5-CH_B); 4.80 (1H, d, J= 4.8, 8-CH); 4.82–5.11 (3H, br. s, OH and NCH_2); 5.25 (1H, d, J_{cis} = 5.2) and 5.43 (1H, d, J_{trans} = 17.0, CH=C$\underline{H}_2$); 5.95 (1H, s, H-3 Fur); 6.01–6.18 (1H, m, C$\underline{H}$=CH_2); 6.28 (1H, s, H-4 Fur); 7.38 (1H, s, H-5 Fur). Mass spectrum, m/z (I_{rel}, %): 366 $[M]^+$ (3), 348 $[M–H_2O]^+$ (3), 323 $[M–CH_3CO]^+$ (9), 306 $[M+H–H_2O–CH_3CO]^+$ (23), 305 $[M–H_2O–CH_3CO]^+$ (100), 265 (13), 44 $[CH_3CO]^+$ (38), 42 (28). Found, %: C 68.70; H 5.88; N 7.59. $C_{21}H_{22}N_2O_4$. Calculated, %: C 68.84; H 6.05; N 7.65.

2-[7-Acetyl-4-cyano-6-hydroxy-1,6-dimethyl-8-(4-methylphenyl)-5,6,7,8-tetrahydroisoquinolin-3-yl]-2-benzylmalononitrile (9). Yield 0.60 g (60%), white needles, mp 208–210°C IR spectrum, ν, cm^{-1}: 3455 (OH), 2213 (CN), 1687 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.33 (3H, s, CH_3); 2.06 (3H, s, CH_3); 2.10 (3H, s, CH_3); 2.29 (3H, s, CH_3); 2.99 (1H, d, J = 10.1, 7-CH); 3.07 (1H, d, J = 17.4) and 3.33 (1H, d, J=17.4, 5-CH_2); 3.76 (1H, d, J = 14.0) and 3.82 (1H, d, J = 14.0, C$\underline{H}_2$Ph); 4.55 (1H, d, J = 10.1, 8-CH); 4.77 (1H, br. s, OH); 6.86 (2H, d, J = 7.5, H Ar); 7.05 (2H, d, J = 7.5, H Ar); 7.32–7.41 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 21.1; 25.0; 28.1; 31.7; 42.8; 43.3; 44.2; 47.0; 66.5; 68.0; 105.8; 113.5; 113.7; 114.5; 128.6 (2C); 129.1 (2C); 129.2; 129.8 (2C); 130.9 (2C); 132.6; 136.2; 136.3; 140.4; 148.1; 152.2; 161.7; 209.6. Mass spectrum, m/z (I_{rel}, %): 489 $[M+H]^+$ (2), 488 $[M]^+$ (3), 470 $[M–H_2O]^+$ (6), 427 $[M–CH_3CO–H_2O]^+$ (64), 337 (12), 92 $[C_6H_5CH_3]^+$ (12), 91 $[C_6H_5CH_2]^+$ (100), 90 $[C_6H_5CH]^+$ (27), 65 (12), 43 $[CH_3CO]^+$ (48), 32 (7). Found, %: C 76.05; H 5.59; N 11.30. $C_{31}H_{28}N_4O_2$. Calculated, %: C 76.21; H 5.78; N 11.47.

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