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A novel and chemoselective synthesis of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones from *o*-oxiranylmethylbenzonitrile intermediates and TBAB/NaCN

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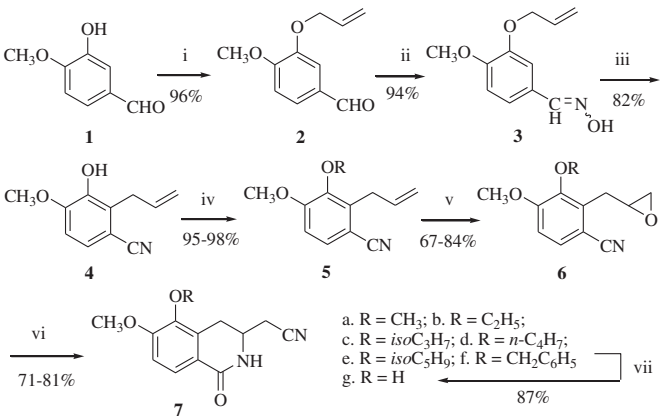
ABSTRACT

A novel synthesis of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones is described. *o*-Oxiranylmethylbenzonitriles, prepared from isovanillin via five synthetic steps, were treated with NaCN/tetra-*n*-butylammonium bromide (TBAB) to yield 3,4-dihydroisoquinolin-1(2*H*)-ones in good yields. This one pot reaction demonstrates the novel and chemoselective nature of ring-opening of epoxide by cyanide to generate an iminoisochroman ring via cyclization, again ring-opening by cyanide to generate a Michael acceptor and a donor, and ring re-cyclization through an intramolecular conjugate addition. The detailed mechanism is also rationally proposed.

1. Introduction

Isoquinolinone, a structural unit of several natural occurring alkaloids,[1] attracts the attention of either synthetic or natural product chemists due to their diverse biological activities.[2] Isoquinolinones are also as the key intermediates for the synthesis of various alkaloids, such as indenoisoquinolines,[3] protoberberines,[4] and dibenzoquinolizines.[5] The traditional synthetic methods of isoquinolinones usually involves the Bischler–Napieralski reaction of *N*-phenethylamides with carbamates,[6] the ring closure of isocyanates with various Lewis acids including $POCl_3$,[7a,b] $SnCl_4$,[7c] BF_3 etherate,[7d,e] as well as the cyclization of carbamates with PPA,[8a] $POCl_3$,[8b] Tf_2O,[8c] or with a mixture of P_2O_5 and $POCl_3$.[8d] Other synthetic strategies include the intramolecular cyclization of acyl radical into the azido group,[9] cobalt carbonyl catalyzed the carbonylation of aryl halides bearing ethyl amino groups on the side chain α to the halogen,[10] and condensation of laterally lithiated *o*-methyl and *o*-ethylbenzamides with imines[11] and others.[12] Despite numerous synthetic methods reported, however, some drawbacks still exist in those reported methods, such as utilization of corrosive acids, tedious reaction conditions, and limitation of substituted congeners. As an extension of our work on benzocyclic and benzoheterocyclic compounds derived from isovanillin,[13] we report here the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones from a one pot reaction of 3-alkoxy-4-methoxy-2-oxiranylmethylbenzonitriles (**6**), which derived from isovanillin via five synthetic steps, with NaCN and TBAB in refluxing acetonitrile (Scheme 1).



Scheme 1. Synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**7**) from isovanillin (**1**). Reactions reagents and conditions: i. allyl bromide, K_2CO_3, acetone, reflux, 5 h; ii. $NH_2OH/EtOH/H_2O$; iii. phthalic anhydride, 160 °C, 5 min and then 180 °C, 2 h; iv. RI(Br), K_2CO_3 acetone, reflux, 8 h; v. *m*-CPBA, CH_2Cl_2, rt, 17 h; vi. NaCN, TBAB, CH_3CN, reflux, 13 h; vii. 20% $Pd(OH)_2/C$, cyclohexene, ethanol, reflux, 4 h.

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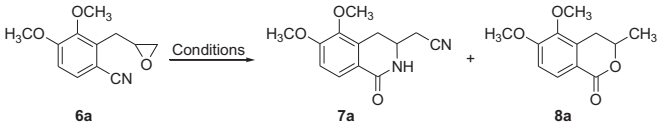
2. Results and discussion

As shown in Scheme 1. The key intermediates 3-alkoxy-4-methoxy-2-oxiranylmethylbenzonitriles (**6a**–**f**) were prepared according to the following procedures. Reaction of isovanillin (**1**) with allyl bromide in the presence of K_2CO_3 in refluxing acetone gave 3-allyoxy-4-methoxybenzaldehyde (**2**), in 96% yield. Subsequently, compound **2** was treated with hydroxylamine to undergo oximation to afford 3-allyoxy-4-methoxybenzaldehyde oxime (**3**), in 94% yield. The oxime **3** was then heated with phthalic anhydride to 160 °C for 5 min to yield the *O*-allyloxybenzonitrile,[14] which was not isolated, the mixture was continually heated under vacuum to remove water, which was produced during the former dehydration reaction. The resulting mixture was subsequently heated to 180 °C under argon for 2 h, a Claisen rearrangement condition, to afford 2-allyl-3-hydroxy-4-methoxybenzonitrile (**4**), in 82% yield. Reaction of compound **4** with various alkyl halides led to 2-allyl-3-alkoxy-4-methoxy-benzonitriles (**5a**–**f**), in 95–98% yields. The structures of **5a**–**f** could be simply deduced from their spectral data. The ^{1}H NMR spectrum of compound **5a**, for an example, showed allyl group signals at 3.60 (d, J=6.4 Hz, 2H, ArCH_2CH=CH_2), 5.08 (m, 2H, ArCH$_2$CH=CH_2), and 5.96 (m, 1H, ArCH$_2$CH=CH$_2$); two methoxy signals at 3.83 and 3.92; two near-by aromatic protons doublets at 6.85 and 7.38 with equal *ortho* coupling constant (J=8.6 Hz). Furthemore, other data, such as ^{13}C NMR, EI-MS, and HRMS are all coinsistant with the proposed structure of **5a**. Epoxidation of **5a**–**f** with *m*-CPBA in CH_2Cl_2 at 0 °C gave 3-alkoxy-4-methoxy-2-oxiranyl-methyl benzonitriles (**6a**–**f**) in yields of 67–84%. The structure of **6a**–**f** was also confirmed by their spectral data. For instance, in the ^{1}H NMR spectrum of **6a** showed one epoxy group, which signals appeared at 2.69 (m, 2H), 3.00 (m, 2H), and 3.22 (m, 1H), two methoxy groups at 3.88 and 3.91, and two near-by aromatic protons doublets at 6.86 and 7.38 with the equal *ortho* coupling constant (J=8.8 Hz). As before, the ^{13}C NMR, EI-MS, and elemental analysis results are all consistent with the proposed structure of **6a**. Then, as a model reaction, compound **6a** was reacted with various cyanide nucleophiles including (i) $NaCNBH_3$, (ii) $NaCNBH_3$/trimethylsilyl cyanide (TMSCN), and (iii) NaCN/TBAB to investigate the optimum condition to yield compound **7a**. The various reaction results obtained were presented in Table 1.

As shown in Table 1, when sodium cyanoborohydride was used as the only reagent in refluxing THF, 5,6-dimethoxy-3-methylcyano-3,4-dihydroisoquinolin-1(2*H*)-one **7a** was obtained in 34% yield and with by-product 5,6-dimethoxy-3-methyl-3,4-dihydroisocoumarin **8a**, in 19% yield. Obviously the cyanoborohydride can serve as both a nucleophile to offer cyanide ion to generate **7a** and to offer hydride to yield **8a** (entries 1, 3,–5). When using combination of $NaCNBH_3$ and $NiCl_2$ as nucleophile, the % yield and the selectivity to produce **7a** were not improved (entry 5). Apparently the $NaCNBH_3$ is a nucleophile with little selectivity yielding **7a** and **8a** as competition products. In order to increase the concentration of the nucleophilic cyanide ion, TMSCN was utilized as an additive of $NaCNBH_3$. The result showed that higher selectivity was achieved with 53% yield of **7a** and 4% yield of **8a** (entry 8). When TMSCN was used as the sole nucleophilic reagent, no product of **7a** or **8a** was obtained (entries 6 and 7). This means TMSCN generates cyanide ion only when $NaCNBH_3$ is present. To eliminate the hydride induced product **8a**, we switched $NaBH_3CN$ to NaCN and combined it with TBAB phase transfer catalyst using various ratios. As expected only **7a** was obtained and higher concentration of NaCN (2.4 equiv) gave higher yield of **7a** (71% for entry 10 vs 29% for entry 9). Solvents played an important role too. In the previous synthesis of **7a** and **8a** involving $NaBH_3CN$, no reaction took place when CH_2Cl_2 was used as solvent (entry 2). In the case of NaCN and TBAB, acetonitrile gave the highest yield (entry 10). Other solvents gave lower yields under otherwise the same condition: THF (46%) (entry 11), dioxane (41%) (entry 13), DMF (32%) (entry 14), and CH_2Cl_2 (0%) (entry 12). Therefore the trend of solvent effect favoring this reaction is CH_3CN>THF>dioxane>DMF>>CH_2Cl_2. In the absence of TBAB with NaCN as the sole nucleophile, lower yield of **7a** was obtained (entry 15). But increasing the amount of TBAB from 0.5 to 1.2 or 2.4 equiv (entries 16 and 17) did not improve the % yields of **7a**. Probably the 0.5 equiv TBAB, acting as phase transfer catalyst, is capable to carry enough cyanide ions to complete the reaction. Thus, we found that NaCN (2.4 equiv) and TBAB (0.5 equiv) in a refluxing acetonitrile (entry 10) was found to be the optimum condition to yield **7a**. The reaction mechanism for the formation of compound **7** from **6** could be rationally proposed as follows (Scheme 2): (i) The less hindered side of oxiranyl group of **6** was attacked by cyano anion of TBACN, which generated from TBAB and NaCN, to yield an alkoxide. Subsequent attack of the alkoxide to the cyano group of benzonitrile (**6**) gave the cyclized transient product with isochroman ring (**I**). (ii) Then, the acidic hydrogen next to the cyano group on isochroman (**I**) was abstracted by cyanide ion, again generated from TBAB and NaCN, to yield the sodium salts of isochroman **II**. (iii) Followed by picking up a proton from in situ generated HCN, **II** turned into **III**. (iv) Electron migration resulted the ring-opening transient product **IV** possessing a Michael acceptor (acrylonitrile moiety) and an amido anion. (v) Intramolecular Michael (conjugate) addition by the attack of amido anion to beta-carbon of acrylonitrile moiety gave a sodium salt of 3,4-dihydroisoquinolin-1-one **V**. It then quickly converted into **VI** through resonance. (vi) After quenched with water, substituted 3,4-dihydroisoquino-lin-1(2*H*)-ones (**7**) was obtained.

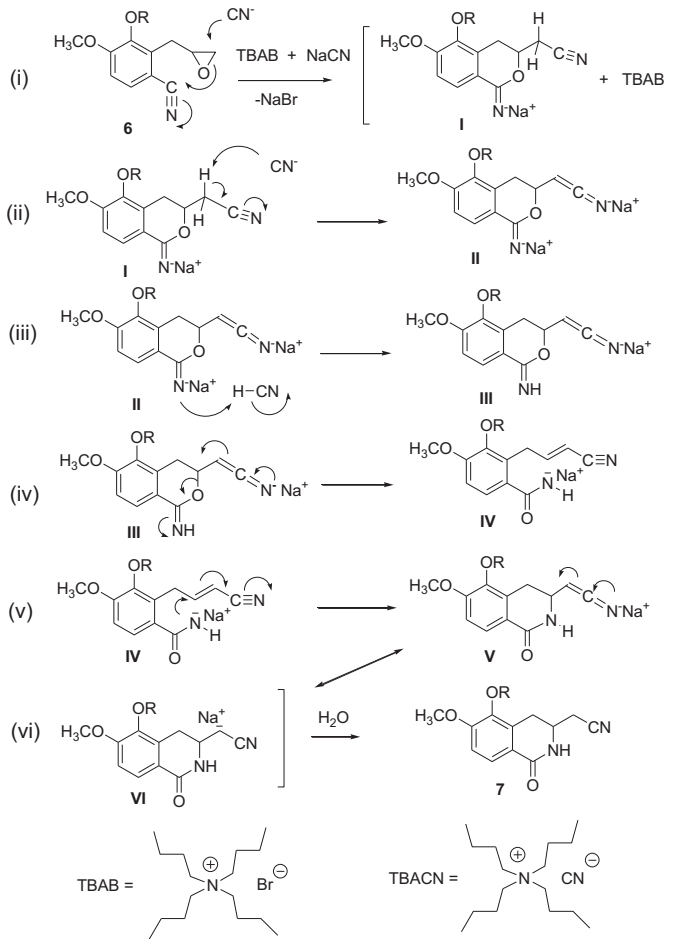
Based on the optimum condition (entry 10) obtained from Table 1, a series of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones (**7a**–**f**) were prepared in moderate to good yields (71–81%). All **7a**–**f** obtained have satisfactory spectral data to support the correctness of their structures. The IR spectrum of **7c**, for example, showed signals at 2199 cm^{-1} (cyano group) and 1678 cm^{-1} (carbonyl on six-membered lactam). The ^{1}H NMR spectrum of **7c** revealed an

Table 1
Various reaction conditions[a] for yielding compound **7a** and **8a** from **6a**



Entry	Cyanide	Solvent	Additive	**7a** (%)[c]	**8a** (%)[c]
1[a]	$NaBH_3CN$ (5 equiv)	THF	None	34	19
2[a]	$NaBH_3CN$ (5 equiv)	CH_2Cl_2	None	0[d]	0
3[a,e]	$NaBH_3CN$ (5 equiv)	EtOH	None	49	36
4[a]	$NaBH_3CN$ (5 equiv)	THF	HCl	20	18
5[a]	$NaBH_3CN$ (5 equiv)	EtOH	$NiCl_2$ 6H_2O	24	13
6[a]	$NaBH_3CN$ (0 equiv)	THF	TMSCN (1 equiv)	0[d]	0
7[a]	$NaBH_3CN$ (0 equiv)	EtOH	TMSCN (1 equiv)	0[d]	0
8[a]	$NaBH_3CN$ (2.5 equiv)	EtOH	TMSCN (2.5 equiv)	53	4
9[b]	NaCN (1.2 equiv)	CH_3CN	TBAB (0.5 equiv)	29	—
10[b]	NaCN (2.4 equiv)	CH_3CN	TBAB (0.5 equiv)	71	—
11[b]	NaCN (2.4 equiv)	THF	TBAB (0.5 equiv)	46	—
12[b]	NaCN (2.4 equiv)	CH_2Cl_2	TBAB (0.5 equiv)	0[d]	—
13[b]	NaCN (2.4 equiv)	Dioxane	TBAB (0.5 equiv)	41	—
14[b]	NaCN (2.4 equiv)	DMF	TBAB (0.5 equiv)	32	—
15[b]	NaCN (2.4 equiv)	CH_3CN	TBAB (0 equiv)	57	—
16[b]	NaCN (2.4 equiv)	CH_3CN	TBAB (1.2 equiv)	69	—
17[b]	NaCN (2.4 equiv)	CH_3CN	TBAB (2.4 equiv)	62	—

[a] The reaction is carried out under reflux for 15 h.
[b] Reflux for 13 h.
[c] The yields are determined after isolating the products from column chromatography.
[d] Only starting material recovered.
[e] The preparation procedure is given in Experimental.



Scheme 2. The proposed mechanism for the formation of **7** from **6**.

isopropoxy group at 1.29 (d, J=6.0 Hz, 6H, ArOCHMe_2) and 4.51 (hept, J=6.0 Hz, 1H, ArOCHMe$_2$), one methoxy group at 3.91 (s, 3H, ArOCH$_3$), two aromatic protons at 6.92 (d, J=8.8 Hz, 1H, ArH), and 7.83 (d, J=8.8 Hz, 1H, ArH). The ^{13}C NMR spectrum of **7c**, which exhibited fifteen carbons, and the molecular ion peak at m/z=274 found in EI-MS spectrum, are all consistent with the structure for **7c**. The only OH-bearing derivative, **7g**, is obtained from the benzylation of **7f**. The physical and spectral data of **7a**–**g** are summarized in Table 2.

In addition, these structures (**7a**–**g**) were also supported by the ^{13}C NMR data. One member of this series, 5,6-dimeth-oxy-3-methylcyano-3,4-dihydroisoquinolin-1(2*H*)-one (**7a**) was also confirmed by X-ray diffraction method (Fig. 1).

3. Conclusion

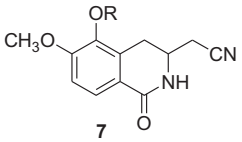
We have established a unique chemoselective synthesis of a series of 3,4-dihydroisoquinolin-1(2*H*)-ones bearing multiple functional groups including cyano group and amide group (**7a**–**f**), or even phenolic OH (**7g**) from the reaction of 3-alkoxy-4-methoxy-2-oxiranylmethylbenzonitriles with NaCN/TBAB in fairly good yields.

4. Experimental

4.1. General

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. IR spectra were run on a Perkin–Elmer spectrometer. Elemental analyses were recorded on a Heraeus CHN–O Rapid analyzer. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230–400 mesh) for column chromatography and precoated silica gel plates (60 F_{254}) for TLC were purchased from E.

Table 2
The selected physical and spectral data of substituted 3-methylcyano-6-methoxy-3,4-dihydroisoquinolin-(2*H*)-1-ones (**7a**–**g**)



a. R = CH_3; b. R = C_2H_5;
c. R = *iso*C_3H_7; d. R = *n*-C_4H_7;
e. R = *iso*C_5H_9; f. R = $CH_2C_6H_5$;
g. R = H

Compd	Yield[a] (%)	Mp (°C)	IR (cm^{-1}) (C=O) (CN) (NH)	HRMS formula calcd found	EA calcd found (C%; H%; N%)
7a	71	155–156	1679 2250 3162	$C_{13}H_{14}N_2O_3$ 246.0999 246.1001	63.40; 5.73; 11.38 63.44; 5.92; 10.98
7b	81	198–199	1675 2249 3193	$C_{14}H_{16}N_2O_3$ 260.1155 260.1158	64.60; 6.20; 10.76 64.45; 6.20; 10.71
7c	77	143–144	1678 2199 3206	$C_{15}H_{18}N_2O_3$ 274.1312 274.1314	65.68; 6.61; 10.21 65.62; 6.75; 10.01
7d	80	154–155	1670 2251 3195	$C_{16}H_{20}N_2O_3$ 288.1468 288.1470	66.65; 6.99; 9.72 66.32; 7.03; 9.63
7e	73	142	1676 2252 3162	$C_{17}H_{22}N_2O_3$ 302.1625 302.1628	67.53; 7.33; 9.26 67.44; 7.39; 9.22
7f	75	170–171	1664 2248 3173	$C_{19}H_{18}N_2O_3$ 322.1317 322.1315	70.79; 5.63; 8.69 70.67; 5.70; 8.65
7g	87	135–136	1664 2248 3177 3404 (OH)	$C_{12}H_{12}N_2O_3$ 232.0848 232.0849	62.06; 5.21; 12.06 61.83; 5.27; 12.05

[a] Isolated from column chromatography.

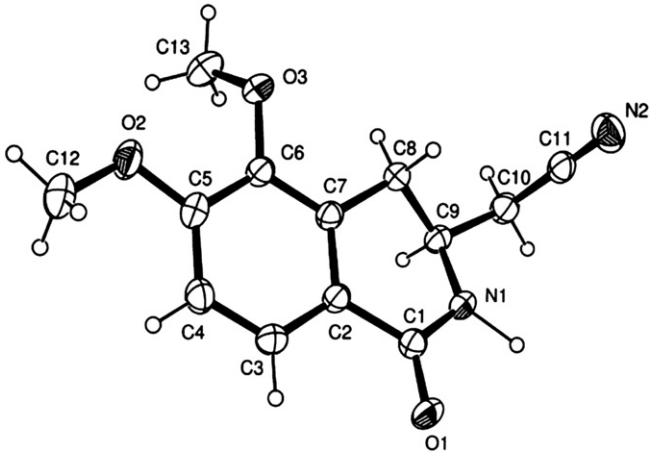


Fig. 1. X-ray crystal structure of 5,6-dimethoxy-3-methyl- cyano-3,4-dihydroisoquinolin-1(2*H*)-one (**7a**).

Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

4.2. The preparation of 2-allyl-3-hydroxy-4-methoxy-benzonitrile (4)

Isovanillin (**1**) (15.2 g, 100 mmol) was reacted with allyl bromide (14.52 g, 120 mmol) in refluxing acetone for 5 h to give *O*-allylisovanillin (**2**) (18.43 g, 96%). Followed by treating with hydroxylamine [generated from hydroxyl-ammonium chloride (8.34 g, 120 mmol) and NaOH (4.80 g, 120 mmol) in H_2O (50 mL)], compound **2** was converted into corresponding oxime **3** (11.67 g, 94%). Treating **3** (11 g, 53 mmol) with phthalic anhydride (7.87 g, 53 mmol) at fused state (160 °C) for 5 min gave a benzonitrile, which was not isolated. After removing the forming water by suction, the reaction mixture was further heated to 180 °C under argon for 2 h to afford the Claisen rearrangement product 2-allyl-3-hydroxy-4-methoxybenzonitrile **4** in one pot. The crude product was purified from column chromatography (ethyl acetate/*n*-hexane=1:15) to give pure **4**. Compound **4** (8.23 g, 82%) was obtained as colorless crystals, mp 91.5 °C (lit.[14] mp 91.5 °C), R_f=0.30 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.60 (d, J=6.4 Hz, 2H, ArCH_2CH=CH_2), 3.94 (s, 3H, $ArOCH_3$), 5.04 (m, 2H, $ArCH_2CH$=CH_2), 5.84 (s, 1H, ArOH), 5.97 (m, 1H, $ArCH_2CH$=CH_2), 6.79 (d, J=8.4 Hz, 1H, ArH), 7.21 (d, J=8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5, 56.2, 156.6, 108.8, 116.2, 118.3, 125.5, 129.0, 134.2, 143.8, 149.8; EI-MS (70e V) m/z (rel intensity, %) 189 (M^+, 14), 188 (97), 174 (67), 147 (40), 146 (100), 129 (31), 128 (30); HRMS calcd for $C_{11}H_{11}NO_2$: 189.0790. Found: 189.0792.

4.3. General procedure for the preparation of 2-allyl-3-alkoxy-4-methoxy-benzonitriles (5a–f)

To a solution of 2-allyl-3-hydroxy-4-methoxybenzonitrile (**4**) (1.89 g, 10 mmol) dissolved in acetone (100 mL), K_2CO_3 (1.66 g, 12 mmol) and alkyl halide (12 mmol) were added sequentially. The reaction mixture was refluxed for 8 h (monitored by TLC). After the end of reaction, the mixture was filtered from Celite 545 to remove solid. The filtrate was dried in vacuo to afford crude 2-allyl-3-alkoxy-4-methoxybenzonitriles (**5a**–**f**). After purification by column chromatography (ethyl acetate/*n*-hexane=1:15), pure **5a**–**f** were obtained.

*4.3.1. 2-Allyl-3,4-dimethoxybenzonitrile (**5a**).* Compound **5a** (1.99 g, 98%) was obtained as colorless liquid, R_f=0.56 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.60 (d, J=6.4 Hz, 2H, ArCH_2CH=CH_2), 3.83 (s, 3H, $ArOCH_3$), 3.92 (s, 3H, $ArOCH_3$), 5.08 (m, 2H, $ArCH_2CH$=CH_2), 5.96 (m, 1H, $ArCH_2CH$=CH_2), 6.85 (d, J=8.6 Hz, 1H, ArH), 7.38 (d, J=8.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.8, 55.8, 60.9, 105.1, 110.6, 116.4, 118.1, 129.6, 134.9, 137.4, 147.3, 156.5; EI-MS (70 eV) m/z (rel intensity, %) 203 (M^+, 54), 188 (81), 161 (100), 145 (35), 133 (37), 132 (61), 128 (47); HRMS calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0943.

*4.3.2. 2-Allyl-3-ethoxy-4-methoxybenzonitrile (**5b**).* Compound **5b** (2.10 g, 97%) was obtained as colorless liquid, R_f=0.59 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (t, J=7.0 Hz, 3H, $ArOCH_2CH_3$), 3.61 (d, J=6.2 Hz, 2H, ArCH_2CH=CH_2), 3.90 (s, 3H, $ArOCH_3$), 4.03 (q, J=7.0 Hz, 2H, $ArOCH_2CH_3$), 5.07 (m, 2H, $ArCH_2CH$=CH_2), 5.95 (m, 1H, $ArCH_2CH$=CH_2), 6.83 (d, J=8.6 Hz, 1H, ArH), 7.37 (d, J=8.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5, 32.9, 55.8, 69.0, 105.0, 110.5, 116.2, 118.1, 129.3, 134.9, 137.4, 146.4, 156.5; EI-MS (70 eV) m/z (rel intensity, %) 217 (M^+, 41), 202 (59), 188 (57), 174 (52), 146 (100), 129 (33), 128 (76); HRMS calcd for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1097.

*4.3.3. 2-Allyl-3-isopropoxy-4-methoxybenzonitrile (**5c**).* Compound **5c** (2.24 g, 97%) was obtained as colorless liquid, R_f=0.63 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (d, J=6.2 Hz, 6H, $ArOCHMe_2$), 3.61 (d, J=6.2 Hz, 2H, ArCH_2CH=CH_2), 3.88 (s, 3H, $ArOCH_3$), 4.58 (hept, J=6.2 Hz, 1H, $ArOCHMe_2$), 5.07 (m, 2H, $ArCH_2CH$=CH_2), 5.93 (m, 1H, $ArCH_2CH$=CH_2), 6.83 (d, J=8.8 Hz, 1H, ArH), 7.38 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.8, 22.3, 32.9, 55.5, 104.9, 110.3, 116.1, 118.5, 128.7, 134.4, 137.3, 144.8, 156.3; EI-MS (70 eV) m/z (rel intensity, %) 231 (M^+, 7), 189 (77), 174 (80), 157 (32), 146 (100), 129 (30), 128 (34); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1254.

*4.3.4. 2-Allyl-3-n-butoxy-4-methoxybenzonitrile (**5d**).* Compound **5d** (2.32 g, 95%) was obtained as colorless liquid, R_f=0.65 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.98 (t, J=7.4 Hz, 3H, $ArOCH_2CH_2CH_2CH_3$), 1.50 (sixt, J=7.4 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 1.75 (quint, J=7.4 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 3.60 (d, J=6.2 Hz, 2H, ArCH_2CH=CH_2), 3.89 (s, 3H, $ArOCH_3$), 3.95 (t, J=7.4 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 5.07 (m, 2H, $ArCH_2CH$=CH_2), 5.94 (m, 1H, $ArCH_2CH$=CH_2), 6.83 (d, J=8.8 Hz, 1H, ArH), 7.35 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$,50 MHz) δ 19.0, 32.1, 32.8, 37.6, 55.7, 73.0, 105.0, 110.5, 116.2, 118.0, 129.2, 134.8, 137.3, 146.5, 156.5; EI-MS (70 eV) m/z (rel intensity, %) 245 (M^+, 22), 189 (58), 174 (92)., 157 (44), 146 (100), 129 (28), 128 (35); HRMS calcd for $C_{15}H_{19}NO_2$: 245.1416. Found: 245.1412.

*4.3.5. 2-Allyl-3-isopentoxy-4-methoxybenzonitrile (**5e**).* Compound **5e** (2.49 g, 96%) was obtained as colorless liquid, R_f=0.67 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (d, J=6.6 Hz, 6H, $ArOCH_2CH_2CHMe_2$), 1.69 (q, J=6.6 Hz, 2H, $ArOCH_2CH_2CHMe_2$), 1.85 (m, 1H, $ArOCH_2CH_2CHMe_2$), 3.60 (d, J=6.2 Hz, 2H, ArCH_2CH=CH_2), 3.90 (s, 3H, $ArOCH_3$), 3.98 (t, J=6.6 Hz, 2H, $ArOCH_2CH_2CHMe_2$), 5.06 (m, 2H, $ArCH_2CH$=CH_2), 5.95 (m, 1H, $ArCH_2CH$=CH_2), 6.83 (d, J=8.8 Hz, 1H, ArH), 7.35 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 24.7, 32.8, 38.9, 55.7, 71.8, 105.5, 110.5, 116.2, 118.1, 129.2, 134.9, 137.3, 146.6, 156.5; EI-MS (70 eV) m/z (rel intensity, %) 259 (M^+, 20), 189 (88), 174 (100), 157 (50), 146 (80), 129 (27), 128 (25); HRMS calcd for $C_{16}H_{21}NO_2$:259.1567. Found: 259.1571.

*4.3.6. 2-Allyloxy-3-benzyloxy-4-methoxybenzonitrile (**5f**).* Compound **5f** (2.65 g, 95%) was obtained as yellow liquid, R_f=0.65 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.55 (d, J=6.2 Hz, 2H, ArCH_2CH=CH_2), 3.92 (s, 3H, $ArOCH_3$), 4.95 (m, 2H, $ArCH_2CH$=CH_2), 5.00 (s, 2H, $ArOCH_2C_6H_5$), 5.95 (m, 1H, $ArCH_2CH$=CH_2), 6.95 (d, J=8.4 Hz, 1H, ArH), 7.40 (m, 5H, ArH), 6.95 (d, J=8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.9, 55.8, 74.8, 109.8, 110.6, 115.6, 116.4, 127.9, 128.1, 128.3, 128.4, 129.0, 129.7, 134.8, 137.0, 146.0, 156.5, 157.5; EI-MS (70 eV) m/z (rel intensity, %) 279 (M^+, 11), 264 (8), 188 (13), 117 (20), 92 (8), 91 (100), 65 (14); HRMS calcd for $C_{18}H_{17}NO_2$: 279.1259. Found: 279.1258.

4.4. General procedure for the preparation of 2-allyl-3-alkoxy-2-oxiranylmethylbenzonitriles (6a–f)

3-Chloroperoxybenzoic acid (1.70 g, 9.84 mmol) dissolved in CH_2Cl_2 (100 mL) was stirred and cooled at 0 °C. To this cold solution was added the CH_2Cl_2 (50 mL) solution of 2-allyl-3-alkoxy-4-methoxybenzonitriles (**5a**–**f**) (9.84 mmol) dropwise. The resulting mixture was continuously stirred at ambient temperature for 17 h. Then, the reaction mixture was washed with NaOH solution (5 g, in H_2O 150 mL) to remove the 3-chlorobenzoic acid formed. The aqueous layer was extracted with CH_2Cl_2 (30 mL×3). Then, all

CH_2Cl_2 layers were combined and washed with brine (20 mL×2), dried with $MgSO_4$, and filtered subsequently. The filtrate was later dried in vacuo and purified from column chromatography (ethyl acetate/*n*-hexane=1:15) to give pure **6a**–**f**.

*4.4.1. 3,4-Dimethoxy-2-oxiranylmethylbenzonitrile (**6a**).* Compound **6a** (1.75 g, 81%) was obtained as colorless crystals, mp 49–50 °C, R_f=0.36 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.69 (m, 2H, ArH_2CHCOCH$_2$), 3.00 (m, 2H, ArH$_2$CHCOCH_2), 3.22 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.88 (s, 3H, ArOCH$_3$), 3.91 (s, 3H, ArOCH$_3$), 6.86 (d, *J*=8.8 Hz, 1H, ArH), 7.38 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.6, 47.0, 51.0, 55.9, 60.9, 105.6, 111.3, 118.1, 139.4, 143.4, 148.0, 156.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 219 (M^+, 84), 176 (85), 174 (37), 161 (100), 160 (58), 146 (51), 130 (37); HRMS calcd for $C_{12}H_{13}NO_3$: 219.0895. Found: 219.0892; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.00; N, 6.25.

*4.4.2. 3-Ethoxy-4-methoxy-2-oxiranylmethylbenzonitrile (**6b**).* Compound **6b** (1.78 g, 83%) was obtained as colorless crystals, mp 54–55 °C, R_f=0.44 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (t, *J*=7.0 Hz, 3H, ArOCH$_2$C*H*$_3$), 2.67 (m, 2H, ArH_2CHCOCH$_2$), 2.95 (m, 2H, ArH$_2$CHCOCH_2), 3.21 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.88 (s, 3H, ArOCH$_3$), 4.05 (q, *J*=7.0 Hz, 2H, ArOCH_2CH$_3$), 6.84 (d, *J*=8.8 Hz, 1H, ArH), 7.34 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5, 31.8, 47.1, 50.9, 55.8, 69.1, 105.4, 111.1, 118.2, 129.2, 134.4, 147.0, 156.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 233 (M^+, 66), 186 (52), 176 (39), 174 (41), 162 (100), 146 (67), 116 (38); HRMS calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1048. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.88; H, 6.51; N, 5.96.

*4.4.3. 3-Isopropoxy-4-methoxy-2-oxiranylmethylbenzonitrile (**6c**).* Compound **6c** (1.75 g, 82%) was obtained as colorless liquid, R_f=0.47 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, *J*=6.2 Hz, 6H, ArOCHMe$_2$), 2.70 (m, 2H, ArH_2CHCOCH$_2$), 3.19 (m, 2H, ArH$_2$CHCOCH_2), 3.35 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.88 (s, 3H, ArOCH$_3$), 4.61 (hept, *J*=6.2 Hz, 1H, ArOC*H*Me$_2$), 6.84 (d, *J*=8.8 Hz, 1H, ArH), 7.35 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 32.4, 47.3, 50.9, 55.8, 75.1, 105.7, 111.1, 118.3, 128.8, 134.9, 145.7, 156.4; EI-MS (70 eV) *m*/*z* (rel intensity, %) 247 (M^+, 7), 205 (58), 187 (23), 186 (37), 174 (36), 162 (100), 146 (49); HRMS calcd for $C_{14}H_{17}NO_3$: 247.1208. Found: 247.1207.

*4.4.4. 3-Butoxy-4-methoxy-2-oxiranylmethylbenzonitrile (**6d**).* Compound **6d** (1.42 g, 67%) was obtained as colorless liquid, R_f=0.54 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99 (t, *J*=7.4 Hz, 3H, ArOCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.53 (sixt, *J*=7.4 Hz, 2H, ArOCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.77 (quint, *J*=7.4 Hz, 2H, ArOCH$_2$C*H*$_2$CH$_2$CH$_3$), 2.70 (m, 2H, ArH_2CHCOCH$_2$), 2.97 (m, 2H, ArH$_2$CHCOCH_2), 3.24 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.91 (s, 3H, ArOCH$_3$), 4.01 (t, *J*=7.4 Hz, 2H, OCH_2CH$_2$CH$_2$CH$_3$), 6.89 (d, *J*=8.8 Hz, 1H, ArH), 7.37 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 18.9, 31.5, 32.1, 46.8, 50.8, 55.6, 73.0, 105.3, 111.1, 118.0, 129.0, 134.1, 147.0, 156.3; EI-MS (70 eV) *m*/*z* (rel intensity, %) 261 (M^+, 20), 205 (30), 186 (38), 176 (26), 174 (34), 162 (100), 146 (48); HRMS calcd for $C_{15}H_{19}NO_3$: 261.1365. Found: 261.1360.

*4.4.5. 3-Isopentoxy-4-methoxy-2-oxiranylmethylbenzonitrile (**6e**).* Compound **6e** (1.78 g, 84%) was obtained as colorless liquids, R_f=0.58 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (d, *J*=6.6 Hz, 6H, ArOCH$_2$CH$_2$CH*Me*$_2$), 1.68 (q, *J*=6.6 Hz, 2H, ArOCH$_2$C*H*$_2$CHMe$_2$), 1.85 (m, 1H, ArOCH$_2$CH$_2$C*H*Me$_2$), 2.70 (m, 2H, ArH_2CHCOCH$_2$), 2.97 (m, 2H, ArH$_2$CHCOCH_2), 3.25 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.91 (s, 3H, ArOCH$_3$), 4.03 (t, *J*=6.6 Hz, 2H, ArOCH_2CH$_2$CHMe$_2$), 6.87 (d, *J*=8.8 Hz, 1H, ArH), 7.38 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 24.8, 31.7, 38.9, 47.1, 50.9, 55.8, 71.9, 105.4, 111.1, 118.2, 129.2, 134.3, 147.1, 156.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 275 (M^+, 9), 205 (28), 186 (30), 176 (23), 174 (34), 162 (100), 146 (39); HRMS calcd for $C_{16}H_{21}NO_3$: 275.1516. Found: 275.1518.

*4.4.6. 3-Benzyloxy-4-methoxy-2-oxiranylmethoxybenzonitrile (**6f**).* Compound **6f** (1.94 g, 67%) was obtained as pale yellow liquid, R_f=0.49 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.65 (m, 2H, ArH_2CHCOCH$_2$), 2.94 (m, 2H, ArH$_2$CHCOCH_2), 3.18 (m, 1H, ArH$_2$C*H*COCH$_2$), 3.92 (s, 3H, ArOCH$_3$), 5.06 (s, 2H, ArOCH_2C$_6$H$_5$), 6.90 (d, *J*=8.8 Hz, 1H, ArH), 7.34 (m, 5H, ArH), 7.41 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.7, 47.1, 50.9, 55.9, 74.9, 105.6, 111.2, 118.2, 128.1, 128.2, 128.5, 129.7, 134.8, 136.9, 146.6, 156.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 295 (M^+, 1), 203 (10), 175 (11), 174 (84), 146 (13), 91 (100), 65 (16); HRMS calcd for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1205.

4.5. Concomitant preparation of 5,6-dimethoxy-3-methylcyano-3,4-dihydroisoquinolin-1(2*H*)-one (7a) and 5,6-dimethoxy-3-methyl-3,4-dihydroisocoumarin (8a)

3,4-Dimethoxy-2-oxiranylmethylbenzonitrile (**6a**) (0.44 g, 2 mmol) was dissolved in EtOH (30 mL) and sodium cyanoborohydride (0.63 g, 10 mmol) was added in portions with constant stir. The reaction mixture was then heated to reflux for 15 h (monitored by TLC) before quenched with saturated NH_4Cl solution (30 mL) and dried in vacuo to remove EtOH. The obtained residue was extracted with CH_2Cl_2 (50 mL×3). The extracted solution was combined and washed with brine (30 mL×2), dried with $MgSO_4$, and filtered. The filtrate was dried in vacuo and purified by column chromatography (ethyl acetate/*n*-hexane=1:3) to give pure **8a** and **7a**.

*4.5.1. 5,6-Dimethoxy-3-methylcyano-3,4-dihydroisoquinolin-1(2H)-one (**7a**).* Compound **7a** (0.24 g, 49%) was obtained as colorless crystals, mp 155–156 °C, R_f=0.43 (ethyl acetate); IR_{max} (neat) cm^{-1}: 3183 cm^{-1} (NH), 2250 (CN), 1679 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (dd, *J*=16.8, 7.2 Hz, 1H, H$_a$-4), 2.71 (dd, *J*=16.8, 6.0 Hz, 1H, H$_b$-4), 3.07 (dd, *J*=16.4, 6.8 Hz, 1H, C*H*$_a$H$_b$CN), 3.27 (dd, *J*=16.0, 5.2 Hz, 1H, CH$_a$*H*$_b$CN), 3.84 (s, 3H, ArOCH$_3$), 3.94 (s, 3H, ArOCH$_3$), 4.07 (m, 1H, H-3), 6.93 (d, *J*=8.8 Hz, 1H, ArH), 7.37 (br s, 1H, NH), 7.84 (d, *J*=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 26.5, 47.5, 55.8, 60.7, 110.7, 116.6, 120.8, 125.0, 129.8, 145.4, 156.4, 165.8; EI-MS (70 eV) *m*/*z* (rel intensity, %) 246 (M^+, 58), 206 (100), 191 (78), 120 (18), 92 (67), 77 (35), 63 (39); HRMS calcd for $C_{13}H_{14}N_2O_3$: 246.0999. Found: 246.1001; Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.44; H, 5.92; N, 10.98.

*4.5.2. 5,6-Dimethoxy-3-methyl-3,4-dihydroisocoumarin (**8a**).* Yield (0.16 g, 36%) was obtained as colorless crystals, mp 120–121 °C (lit.[15] mp 127–128 °C), R_f=0.31 (ethyl acetate/*n*-hexane=1:5); IR (neat) ν_{max}: 1707 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz) 1.46 (d, *J*=6.2 Hz, 3H, H-9), 2.66 (dd, *J*=16.8, 11.4 Hz, 1H, H$_b$-4), 3.13 (dd, *J*=16.8, 3.2 Hz, 1H, H$_a$-4), 3.78 (s, 3H, ArOCH$_3$), 3.89 (s, 3H, ArOCH$_3$), 4.59 (m, 1H, H-3), 6.88 (d, *J*=8.4 Hz, 1H, ArH), 7.82 (d, *J*=8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) 20.9, 29.0, 55.8, 60.5, 74.6, 110.7, 117.8, 127.2, 133.0, 144.5, 156.7, 165.3; EI-MS (70 eV) *m*/*z* (rel intensity, %) 222 (M^+, 72), 179 (16), 178 (38), 163 (18), 150 (100), 135 (17), 91 (13); HRMS calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0887; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.41.

4.6. General preparation of 5-alkoxy-3-methylcyano-6-methoxy3,4-dihydroisoquinolin-1(2*H*)-ones (7a–f)

To a solution of 3-alkoxy-4-methoxy-2-oxiranylmethylbenzonitriles (**6a**–**f**) (2 mmol) dissolved in CH_3CN (30 mL), sodium cyanide (0.24 g, 4.8 mmol) and tetra-*n*-butylammonium bromide (0.32 mL, 1 mmol) were added in portions sequentially. The reaction

mixture was heated to reflux for 13 h (monitored by TLC) and quenched with saturated NH_4Cl solution (30 mL), solvent was removed in vacuo afterward. The obtained residue was extracted with CH_2Cl_2 (50 mL×3). The extracted solution was combined and washed with brine (30 mL×2), dried with $MgSO_4$, and filtered subsequently. The filtrate was dried in vacuo and purified by column chromatography (ethyl acetate/*n*-hexane=1:3) to afford pure **7a**–**f**.

*4.6.1. 5,6-Dimethoxy-3-methylcyano-3,4-dihydroisoquino-lin-1(2H)-one (**7a**).* The analyzed data for **7a** (0.35 g, 71%) was described previously in 4.5.1 of this experimental section.

*4.6.2. 5-Ethoxy-3-methylcyano-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**7b**).* Compound **7b** (0.42 g, 81%) was obtained as colorless crystals, mp 198–199 °C, R_f=0.42 (ethyl acetate); IR_{max} (neat) cm^{-1}: 3193 cm^{-1} (NH), 2249 (CN), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, J=7.2 Hz, 3H, $ArOCH_2CH_3$), 2.63 (dd, J=16.8, 6.8 Hz, 1H, H_a-4), 2.70 (dd, J=16.8, 6.0 Hz, 1H, H_b-4), 3.08 (dd, J=16.4, 6.8 Hz, 1H, CH_aH_bCN), 3.26 (dd, J=16.4, 5.2 Hz, 1H, CH_aH_bCN), 3.92 (s, 3H, $ArOCH_3$), 4.05 (q, J=7.2 Hz, 2H, $ArOCH_2CH_3$), 4.06 (m, 1H, H-3), 6.92(d, J=8.8 Hz, 1H, ArH), 7.10 (br s, 1H, NH), 7.83 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 23.8, 26.8, 47.6, 55.8, 68.9, 110.6, 116.6, 120.8, 124.9, 130.0, 144.4, 156.5, 165.7; EI-MS (70 eV) *m*/*z* (rel intensity, %) 260 (M^+, 46), 192 (100), 191 (25), 160 (26), 92 (37), 77 (26), 63 (25); HRMS calcd for $C_{14}H_{16}N_2O_3$: 260.1155. Found: 260.1158; Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.20; N, 10.71.

*4.6.3. 5-Isopropoxy-3-methylcyano-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**7c**).* Compound **7c** (0.42 g, 77%) was obtained as colorless crystals, mp 143–144 °C, R_f=0.45 (ethyl acetate); IR_{max} (neat) cm^{-1} : 3206 cm^{-1} (NH), 2199 (CN), 1678 cm^{-1}(C=O), 2199 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, J=6.0 Hz, 6H, $ArOCHMe_2$), 2.62 (dd, J=16.8, 7.2 Hz, 1H, H_a-4), 2.68 (dd, J=16.8, 6.0 Hz, 1H, H_b-4), 3.02 (dd, J=16.0, 6.8 Hz, 1H, CH_aH_bCN), 3.25 (dd, J=16.0, 5.2 Hz, 1H, CH_aH_bCN), 3.91 (s, 3H, $ArOCH_3$), 4.03 (m, 1H, H-3), 4.51 (hept, J=6.0 Hz, 1H, $ArOCHMe_2$), 6.92 (d, J=8.8 Hz, 1H, ArH), 7.29 (br s, 1H, NH), 7.83 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 23.8, 27.4, 29.3, 47.7, 55.7, 74.9, 110.6, 116.6, 120.8, 124.6, 130.4, 143.3, 156.5, 165.8; EI-MS (70 eV) *m*/*z* (rel intensity, %) 274 (M^+, 7), 232 (44), 192 (100), 93 (20), 92 (29), 77 (18), 65 (16); HRMS calcd for $C_{15}H_{18}N_2O_3$: 274.1312. Found: 274.1314; Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.62; H, 6.75; N, 10.01.

*4.6.4. 5-n-Butoxy-3-methylcyano-6-methoxy-3,4-dihydroiso-quinolin-1(2H)-one (**7d**).* Compound **7d** (0.44 g, 80%) was obtained as colorless crystals, mp 154–155 °C, R_f=0.45 (ethyl acetate); IR_{max} (neat) cm^{-1}: 3195 cm^{-1} (NH), 2251 (CN), 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, J=7.2 Hz, 3H, $ArOCH_2CH_2CH_2CH_3$), 1.51 (sixt, J=7.4 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 1.75 (quint, J=6.8 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 2.61 (dd, J=16.8, 6.8 Hz, 1H, H_a-4), 2.68 (dd, J=16.4, 6.0 Hz, 1H, H_b-4), 3.08 (dd, J=16.4, 6.4 Hz, 1H, CH_aH_bCN), 3.26 (dd, J=16.4, 5.2 Hz, 1H, CH_aH_bCN), 3.92 (s, 3H, $ArOCH_3$), 3.97 (t, J=6.8 Hz, 2H, $ArOCH_2CH_2CH_2CH_3$), 4.05 (m, 1H, H-3), 6.89 (br s, 1H, NH), 6.92 (d, J=8.8 Hz, 1H, ArH), 7.83 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 19.2, 23.9, 26.8, 32.3, 47.6, 55.8, 73.2, 110.7, 116.5, 120.8, 124.8, 129.8, 144.7, 156.5, 165.6; EI-MS (70 eV) *m*/*z* (rel intensity, %) 288 (M^+, 12), 232 (32), 193 (11), 192 (100), 191 (12), 177 (7), 160 (19); HRMS calcd for $C_{16}H_{20}N_2O_3$: 288.1468. Found: 288.1470; Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.32; H, 7.03; N, 9.63.

*4.6.5. 5-Isopentyloxy-3-methylcyano-6-methoxy-3,4-dihy-droisoquinolin-1(2H)-one (**7e**).* Compound **7e** (0.44 g, 73%) was obtained as colorless crystals, mp 142 °C, R_f=0.50 (ethyl acetate); IR_{max} (neat) cm^{-1} : 3162 cm^{-1} (NH), 2252 cm^{-1} (CN), 1676 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, J=6.4 Hz, 6H, $ArOCH_2CH_2CHMe_2$), 1.67 (q, J=6.8 Hz, 2H, $ArOCH_2CH_2CHMe_2$), 1.85 (m, 1H, $ArOCH_2CH_2CHMe_2$), 2.63 (dd, J=16.4, 6.8 Hz, 1H, H_a-4), 2.70 (dd, J=16.4, 6.0 Hz, 1H, H_b-4), 3.07 (dd, J=16.4, 6.8 Hz, 1H, CH_aH_bCN), 3.26 (dd, J=16.4, 5.2 Hz, 1H, CH_aH_bCN), 3.92 (s, 3H, $ArOCH_3$), 3.98 (t, J=6.8 Hz, 2H, $ArOCH_2CH_2CHMe_2$), 4.06 (m, 1H, H-3), 6.92 (d, J=8.4 Hz, 1H, ArH), 7.29 (br s, 1H, NH), 7.83 (d, J=8.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 22.6, 23.8, 24.9, 26.7, 39.0, 47.6, 55.7, 71.8, 110.7, 116.6, 120.8, 124.8, 129.8, 144.7, 156.4, 165.8; EI-MS (70 eV) *m*/*z* (rel intensity, %) 302 (M^+, 11), 233 (9), 232 (45), 193 (12), 192 (100), 191 (20), 160 (18); HRMS calcd for $C_{17}H_{22}N_2O_3$: 302.1625. Found: 302.1628; Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.44; H, 7.39; N, 9.22.

*4.6.6. 5-Benzyloxy-3-methylcyano-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**7f**).* Compound **7f** (0.47 g, 75%) was obtained as colorless crystals, mp 170–171 °C, R_f=0.49 (ethyl acetate); IR_{max} (neat) cm^{-1}: 3173 cm^{-1} (NH), 2248 cm^{-1} (CN), 1664 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (dd, J=16.8, 6.8 Hz, 1H, H_a-4), 2.48 (dd, J=16.8, 6.4 Hz, 1H, H_b-4), 2.77 (dd, J=16.4, 6.8 Hz, 1H, CH_aH_bCN), 2.96 (dd, J=16.4, 5.2 Hz, 1H, CH_aH_bCN), 3.82 (m, 1H, H-3), 3.97 (s, 3H, $ArOCH_3$), 5.04 (s, 2H, $ArOCH_2C_6H_5$), 6.95 (d, J=8.4 Hz, 1H, ArH), 7.09 (br s, 1H, NH), 7.35 (m, 5H, ArH), 7.84 (d, J=8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 27.0, 23.9, 47.4, 55.8, 74.8, 110.7, 116.6, 120.8, 125.1, 128.4, 128.5, 128.9, 130.4, 136.9, 143.5, 156.4, 165.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 322 (M^+, 3), 304 (4), 216 (6), 160 (4), 92 (10), 91 (100), 65 (8); HRMS calcd for $C_{19}H_{18}N_2O_3$: 322.1317. Found: 322.1315; Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.67; H, 5.70; N, 8.65.

*4.6.7. Preparation of 5-hydroxy-3-methylcyano-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**7g**).* A mixture of compound **7f** (0.35 g, 1.09 mmol), $Pd(OH)_2/C$ (20%, 0.05 g, 0.76 mmol), cyclohexene (0.98 mL), and ethanol (20 mL) was refluxed for 4 h and then purified by column chromatography (ethyl acetate/*n*-hexane=1:1) to give pure **7g**.

Compound (**7g**) (0.22 g, 87%) was obtained as colorless crystals, mp 135–136 °C, R_f=0.37 (ethyl acetate); IR_{max} (neat) cm^{-1}: 3404 cm^{-1} (OH), 3177 cm^{-1} (NH), 2249 cm^{-1} (CN), 1663 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 400 MHz) δ 2.78 (m, 1H, H_a-4), 2.79 (dd, J=16.8, 6.0 Hz, 1H, H_b-4), 2.85 (m, 1H, CH_aH_bCN), 3.12 (dd, J=16.4, 5.2 Hz, 1H, CH_aH_bCN), 3.84 (m, 1H, H-3), 3.89 (s, 3H, OCH_3), 7.00 (d, J=8.4 Hz, 1H, ArH), 7.44 (d, J=8.4 Hz, 1H, ArH), 7.96 (br s, 1H, NH), 9.30 (br s, 1H, ArOH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.4, 26.4, 46.9, 56.3, 110.0, 118.6, 119.8, 121.4, 123.8, 142.7, 151.2, 165.6; EI-MS (70 eV) *m*/*z* (rel intensity, %) 232 (M^+, 47), 193 (11), 192 (100), 177 (22), 161 (6), 160 (51), 132 (7); HRMS calcd for $C_{12}H_{12}N_2O_3$: 232.0848. Found: 232.0849; Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.27; N, 12.05.

4.7. X-ray investigations

A colorless rod plate crystal (0.20×0.20×0.60 mm) of $C_{13}H_{14}N_2O_3$ (**7a**) was obtained by crystallization from ethyl acetate and *n*-hexane. Data collection was performed on a RIGAKU AFC7S diffractometer with a graphite monochromator ($\omega/2\theta$ scans, $2\theta_{max}$=52.0°) at 298 K. The crystal belongs to the monoclinic system, space group $P2_1/c$ (No. 14), with a=7.338(6) Å, b=10.441(6) Å, c=15.846(3) Å, β=90.60(3)°, V=1214.0(12) Å^3, Z=4, D_{calcd}=1.347 Mg/m^3, λ(Mo-Kα)=0.71069 Å. A total of 2379 unique reflections were collected. The structure was solved by direct method and refined by full-matrix least-squares procedure. The non-hydrogen atoms were given anisotropic thermal parameters. The refinement converged to a final R=0.0528 and wR_2=0.145 for 1220 observed reflections [$I>2.00\sigma(I)$] using 167 parameters. Copies of the deposited crystal data (CCDC No. 810680) can

be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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