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$InCl_3$-Catalyzed hetero-Diels–Alder reaction: an expeditious synthesis of pyranoquinolines

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Abstract—Indium trichloride catalyzes efficiently the cycloaddition reactions of aryl amines with 3,4-dihydro-2*H*-pyran (DHP) under mild reaction conditions to afford the corresponding pyrano[3,2-*c*]quinolines in high yields with high diastereoselectivity.

1. Introduction

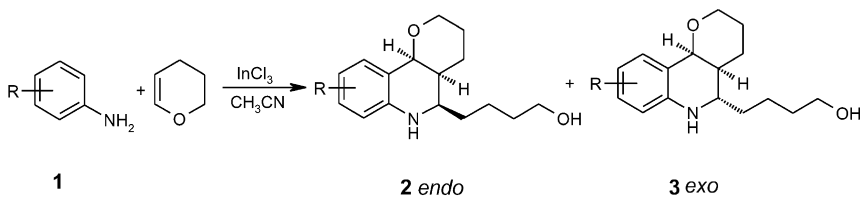
The aza-Diels–Alder reaction is one of the most powerful synthetic routes for constructing nitrogen containing six-membered heterocycles.[1] Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activity[2] including psychotropic, antiallergic, anti-inflammatory and estrogenic activity. In addition, pyranoquinoline derivatives are found to possess a wide range of pharmacological activity.[3] The imino-Diels–Alder reaction provides a useful entry to the preparation of tetrahydroquinoline derivatives. Imines derived from aromatic amines act as heterodienes and undergo imino-Diels–Alder reaction with various dienophiles. Generally, Lewis acids[4–6] are known to catalyze the imino-Diels–Alder reactions to produce quinoline derivatives. Metal triflates[7,8] are also found to be effective Lewis acids in promoting imino-Diels–Alder reactions. However, there are no reports on the one-pot synthesis of pyranoquinolines from aryl imines (generated in situ from aryl amines and 3,4-dihydro-2*H*-pyran) with 3,4-dihydro-2*H*-pyran (DHP).

In recent years, indium trihalides have emerged as mild and water-tolerant Lewis acid imparting high regio- and chemoselectivity in various organic transformations. They can be conveniently used in both aqueous and non-aqueous medium and in addition, they can be recovered from aqueous layer on work-up and recycled for use in subsequent reactions. Furthermore, they are highly efficient to activate nitrogen-containing compounds such as imines and hydrazones, etc.[9,10]

2. Results and discussion

In this report, we describe a novel and highly efficient method for the synthesis of pyrano- and furanoquinolines using a catalytic amount of $InCl_3$. Thus treatment of aniline with 3,4-dihydro-2*H*-pyran (DHP) in the presence of 5 mol% indium trichloride in acetonitrile at ambient temperature afforded the corresponding pyrano[3,2-*c*]-quinoline derivatives **2** and **3** in 85% yield (Scheme 1).

Similarly, several aryl amines reacted smoothly with 3,4-dihydro-2*H*-pyran to give the corresponding pyranoquinolines in 78–90% yield. The reactions proceeded efficiently in high yields at ambient temperature. In most of the cases, the products were obtained as a mixture of *endo* and *exo*-isomers, favoring the *endo*-diastereomer. The product ratio



1 **2** *endo* **3** *exo*

Scheme 1.

Keywords: indium reagents; hetero-Diels–Alder reaction; tetrahydroquinolines.
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Figure 1. Chemical structure and important nOes of compound **2a**.

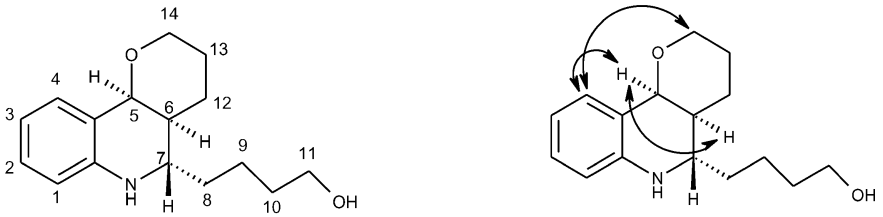


Figure 2. Chemical structure and important nOes of compound **3a**.

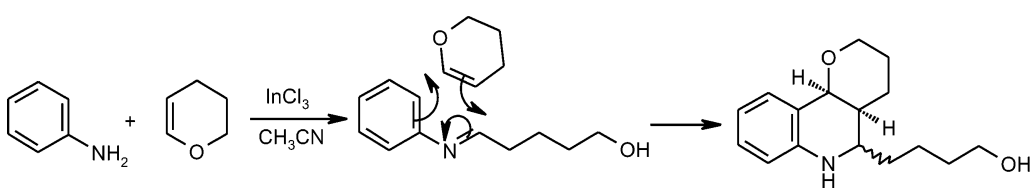
was determined by ^{1}H NMR spectrum of the crude product. The stereochemistry of the product **2a** was assigned on the basis of coupling constants and NOE studies. The two six-membered quinoline and tetrahydropyran rings are *cis*-fused as depicted by the small coupling constant value J_{H5-H6}=5.6 Hz for H_5 (5.0 ppm) proton as well as the observation of nOe cross peak between them in the NOESY spectrum. The middle six-membered quinoline ring conformation is confirmed as a twist conformation, which is consistent with the small coupling constant value J_{H6-H7}= 6.9 Hz, for H_7 (δ 3.34 ppm) and the presence of nOe cross peaks between H_5-H_6, H_6-H_7 in the NOESY spectrum. While the middle six-membered quinoline ring in the twist conformation the six-membered tetrahydropyran ring takes a chair conformation of $^5C_{13}$ (here 5 and 13 are the carbon atoms in the molecule), which is consistent with the large coupling constants values $J_{H14ax-H13ax}$=11.9 Hz for H_{14ax} (δ 3.39 ppm), $J_{H6-H12ax}$=12.1 Hz for H_6 (δ 2.00 ppm) as well as the presence of nOe cross peak between H_4-H_{14ax} (as shown in Fig. 1) and absence of nOe cross peak between H_5-H_{14} in the NOESY spectrum (Fig. 2).

In *exo* isomer **3a** also, like *endo* isomer **2a**, the two six-membered quinoline and tetrahydropyran rings are *cis*-fused as depicted by the small coupling constant value J_{H5-H6}= 3.2 Hz for H_5 (4.42 ppm) proton as well as the observation of nOe cross peak between them and the absence of nOe cross peak between H_6-H_7 in the NOESY spectrum. The reactions are clean and highly diastereoselective, affording the corresponding *endo* **2** with only a minor amount of the other *exo* **3**. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. This method is equally effective with electron rich as well as electron deficient anilines. There are several advantages in the use of indium trichloride for this transformation, which include mild reaction conditions, improved yields, enhanced selectivity, simplicity in operation and work-up conditions. This method does not require anhydrous solvents or stringent reaction conditions whilst no precautions need to be taken to exclude moisture from the reaction medium. The solvent acetonitrile appears to be superior affording best yields. The reaction may proceed via an imino-Diels–Alder process between 2-azadiene (formed in situ from cyclic enol ether and aniline) and another equivalent of enol ether resulting in the formation of fused quinoline derivatives (Scheme 2).

The scope and generality of this process is illustrated with respect to various substituted anilines and cyclic enol ethers and the results are presented in Table 1.

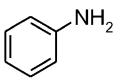
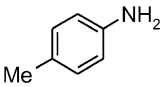
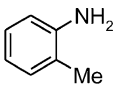
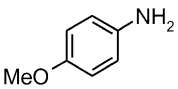
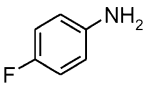
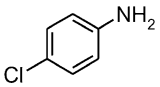
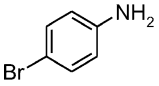
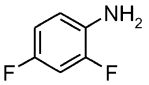
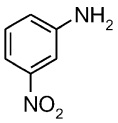
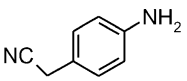
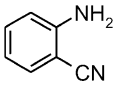
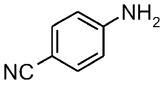
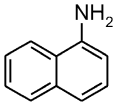
3. Conclusion

In summary, the paper describes a novel and highly efficient method for the synthesis of pyranoquinoline derivatives from aryl amines and 2 equiv. of cyclic enol ether using a catalytic amount of indium trichloride. The notable features of this procedure are mild reaction conditions, greater selectivity, improved yields, cleaner reaction profiles, enhanced rates and operational simplicity which make it a useful and attractive process for the synthesis of fused pyrano[3,2-*c*]quinolines of biological importance.



Scheme 2.

Table 1. $InCl_3$-catalyzed synthesis of tetrahydropyrano[3,2-*c*]quinolines

Entry	Aryl amine	Olefin	Reaction time (h)	Yield (%)[a]	*endo*/*exo*[b]
a			4.0	90	95:5
b			3.5	85	90:10
c			4.0	89	92:8
d			3.5	87	85:15
e			4.5	85	95:5
f			5.0	90	93:7
g			4.5	88	90:10
h			6.0	80	85:15
i			7.0	78	70:30
j			4.5	89	98:2
k			6.0	70	60:40
l			6.0	80	88:12
m			4.0	85	96:4

[a] Isolated and unoptimized yields after column chromatography.
[b] Product ratio was determined by the ^1H NMR spectrum of the crude product.

4. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H and ^{13}C NMR spectra were recorded on Gemini-200 and Unity-500 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer.

4.1. General procedure for the preparation of pyranoquinolines

A mixture of aryl amine **1a** (0.465 g, 5 mmol), dihydropyran (1.0 g, 12 mmol) and $InCl_3$ (5 mol%) in acetonitrile (5 ml) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were concentrated in vacuo and the resulting

product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure tetrahydroquinoline in 90% yield (1.17 g). The aqueous layer was concentrated under reduced pressure to recover the catalyst.

4.1.1. R=H, 4-(3,4,4a,5,6,10b-Hexahydro-2*H*-pyrano-[3,2-*c*]quinolin-5-yl)-1-butanol (2a, 3a). Solid, mp 83–85°C. IR (KBr): ν_{max}: 3360, 2930, 2862, 1615, 1505, 1455, 1300, 1065, 810, 755. EIMS: *m/z*: 261 M^+, 188, 144, 105, 91, 57. Anal. calcd for $C_{16}H_{23}NO_2$ (261.36): C, 73.53%; H, 8.87%; N, 5.36%. Found: C, 73.56%; H, 8.90%; N, 5.38%.

Compound **2a**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J=7.5 Hz, 1H, H_4), 6.96 (t, J=7.5 Hz, 1H, H_3), 6.67 (t, J=7.5 Hz, 1H, H_2), 6.38 (d, J=7.5 Hz, 1H, H_1), 4.98 (d, J=5.7 Hz, 1H, H_5), 3.67 (t, J=6.3 Hz, 2H, H_{11} and $H_{11'}$), 3.60 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{14}), 3.39 (dt, J=2.3, 11.4 Hz, 1H, $H_{14'}$), 3.34 (dt, J=2.2, 7.0 Hz, 1H, H_7), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_6), 1.70–1.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled): δ 145.01, 127.85, 127.51, 120.02, 117.74, 113.79, 72.41, 62.47, 60.63, 54.1, 35.52, 32.59, 31.96, 25.41, 22.14, 17.86.

Compound **3a**: *exo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J=7.5 Hz, 1H, H_4), 6.96 (t, J=7.5 Hz, 1H, H_3), 6.60 (t, J=7.5 Hz, 1H, H_2), 6.42 (d, J=7.5 Hz, 1H, H_1), 4.42 (d, J=3.2 Hz, 1H, H_5), 3.90 (m, 1H), 3.66 (m, 3H), 3.58 (m, 1H), 1.90 (m, 1H, H_6), 1.70–1.32 (m, 10H).

4.1.2. R=*p*-CH_3, 4-(9-Methyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2b, 3b). Solid, mp 79–80°C. IR (KBr): ν_{max}: 3365, 2934, 2862, 1619, 1506, 1461, 1304, 1069, 812, 755. EIMS: *m/z*: 275 M^+, 202, 158, 144, 120, 71, 43. Anal. calcd for $C_{17}H_{25}NO_2$ (275.38): C, 74.14%; H, 9.15%; N, 5.09%. Found: C, 74.17%; H, 9.17%; N, 5.13%.

Compound **2b**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, J=1.5 Hz, 1H, H_1), 6.82 (dd, J=1.5, 7.5 Hz, 1H, H_2), 6.40 (d, J=7.5 Hz, 1H, H_3), 5.00 (d, J=5.7 Hz, 1H, H_4), 3.62 (t, J=6.3 Hz, 2H, H_{11} and H_{11}), 3.58 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{14}), 3.42 (dt, J=2.3, 11.4 Hz, 1H, $H_{14'}$), 3.30 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.22 (s, 3H, CH_3), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled): δ 142.68, 129.67, 128.53, 127.03, 120.02, 114.0, 72.49, 62.48, 60.70, 54.26, 35.64, 32.775, 32.01, 25.38, 22.13, 20.56, 17.81.

Compound **3b**: *exo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, J=1.5 Hz, 1H, H_1), 6.96 (dd, J=1.5, 7.5 Hz, 1H, H_2), 6.52 (d, J=7.5 Hz, 1H, H_3), 4.40 (d, J=3.2 Hz, 1H, H_4), 3.96 (m, 1H), 3.62 (m, 3H), 3.58 (m, 1H), 2.20 (s, 3H, CH_3),1.96 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.3. R=*o*-CH_3, 4-(7-Methyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2c, 3c). Solid, mp 56–57°C. IR (KBr): ν_{max}: 3362, 2930, 2864, 1615, 1505, 1460, 1302, 1065, 810, 755. EIMS: *m/z*: 275 M^+, 216, 203, 158, 144, 117, 71, 41. Anal. calcd for $C_{17}H_{25}NO_2$ (275.38): C, 74.14%; H, 9.15%; N, 5.09%. Found: C, 74.17%; H, 9.17%; N, 5.13%.

Compound **2c**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J=7.5 Hz, 1H, H_3), 6.82 (d, J=7.5 Hz, 1H, H_1), 6.60 (t, J=7.5 Hz, 1H, H_2), 5.00 (d, J=5.5 Hz, 1H, H_4), 3.62 (t, J=6.3 Hz, 2H, H_{11} and $H_{11'}$), 3.56 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{14}), 3.38 (dt, J=2.3, 11.4 Hz, 1H, $H_{14'}$), 3.30 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.10 (s, 3H, CH_3), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled): δ 142.30, 129.87, 128.73, 120.82, 119.45, 116.34, 74.09, 62.16, 53.83, 49.64, 35.93, 32.9, 32.0, 24.0, 22.83, 21.2, 18.4.

4.1.4. R=*p*-OCH_3, 4-(9-Methoxy-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2d, 3d). Viscous oil. IR (KBr): ν_{max}: 3455, 2935, 2845, 1485, 1440, 1260, 1010, 800, 755. EIMS: *m/z*: 291 M^+, 218, 174, 123, 108, 84, 41. Anal. calcd for C_{17} $H_{25}NO_3$ (291.38): C, 70.07%; H, 8.65%; N, 4.81%. Found: C, 70.10%; H, 8.68%; N, 4.85%.

Compound **2d**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, 1H, J=2.6 Hz H_1), 6.66 (dd, J=2.6, 8.0 Hz, 1H, H_3), 6.48 (d, J=8.0 Hz, 1H, H_2), 5.00 (d, J=5.4 Hz, 1H, H_4), 3.74 (s, 3H, OCH_3), 3.68 (t, J=6.3 Hz, 2H, H_{10} and $H_{10'}$), 3.62 (ddt, m, 2H, H_{13} and $H_{13'}$), 3.30 (dt, J=2.6, 7.3 Hz, 1H, H_6), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H).

Compound **3d**: *exo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (d, 1H, J=2.6 Hz, H_1), 6.68 (dd, J=2.6, 8.0 Hz, 1H, H_3), 6.50 (d, J=8.0 Hz, 1H, H_2), 4.44 (d, J=5.4 Hz, 1H, H_4), 3.92 (m, 1H), 3.72 (s, 3H, OCH_3), 3.68 (m, 3H), 3.48 (m, 1H), 1.96 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.5. R=*p*-F, 4-(9-Fluoro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2e, 3e). Solid, mp 110–111°C. IR (KBr): ν_{max}: 3365, 2934, 2862, 1619, 1506, 1461, 1304, 1069, 812, 755. EIMS: *m/z*: 279 M^+, 206, 162, 148, 41. Anal. calcd for $C_{16}H_{22}FNO_2$ (279.35): C, 68.79%; H, 7.94%; F, 6.80%; N, 5.01%. Found: C, 68.82%; H, 7.97%; F, 6.84%; N, 5.06%.

Compound **2e**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, J=2.6, 7.5 Hz, 1H, H_1), 6.70 (d, J=7.5 Hz, 1H, H_2), 6.42 (d, J=7.5 Hz, 1H, H_3), 4.97 (d, J=5.4 Hz, 1H, H_4), 3.62 (t, J=6.3 Hz, 2H, H_{10} and $H_{10'}$), 3.56 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{13}), 3.38 (dt, J=2.3, 11.4 Hz, 1H, $H_{13'}$), 3.25 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled): δ 141.18, 121.64, 114.81, 114.74, 113.60, 113.42, 72.18, 62.41, 60.84, 54.24, 35.18, 32.52, 31.90, 25.22, 22.14, 17.77.

Compound **3e**: *exo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dd, J=2.6, 7.5 Hz, 1H, H_1), 6.78 (d, J=7.5 Hz, 1H, H_2), 6.48 (d, J=7.5 Hz, 1H, H_3), 4.42 (d, J=3.2 Hz, 1H, H_4), 3.86 (m, 1H), 3.66 (m, 2H), 3.48 (m, 1H), 3.35 (m, 1H), 1.90 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.6. R=*p*-Cl, 4-(9-Chloro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2f, 3f). Solid, mp 115–117°C. IR (KBr): ν_{max}: 3356, 2937, 2878, 1472, 1292, 1052, 805, 757. EIMS: *m/z*: 295 M^+, 222, 178, 164, 137, 121, 77, 43. Anal. calcd for $C_{16}H_{22}ClNO_2$ (295.80): C,

64.97%; H, 7.50%; Cl, 11.99%; N, 4.74%. Found: C, 64.99%; H, 7.55%; Cl, 12.02%; N, 4.77%.

Compound **2f**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, J=2.6 Hz, 1H, H_3), 6.96 (dd, J=2.6, 8.0 Hz, 1H, H_2), 6.42 (d, J=8.0 Hz, 1H, H_1), 5.00 (d, J=5.5 Hz, 1H, H_4), 3.70 (t, J=6.3 Hz, 2H, H_{10} and $H_{10'}$), 3.65 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{13}), 3.50 (dt, J=2.3, 11.4, 1H, H_{13}), 3.34 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.02 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 143.58, 129.53, 128.82, 123.50, 122.52, 115.33, 72.98, 66.67, 50.19, 36.09, 32.97, 24.10, 23.03, 22.68, 21.28, 17.87.

Compound **3f**: *exo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J=2.6 Hz, 1H, H_3), 6.98 (dd, J=2.6, 8.0 Hz, 1H, H_2), 6.44 (d, J=8.0 Hz, 1H, H_1), 4.42 (d, J=3.0 Hz, 1H, H_4), 3.86 (m, 1H), 3.65 (m, 3H), 3.50 (m, 1H), 1.88 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.7. R=*p*-Br, 4-(9-Bromo-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2g, 3g). Solid, mp 74–76°C. IR (KBr): ν_{max}: 3350, 2935, 2875, 1598, 1470, 1290, 1055, 803, 755. EIMS: *m*/*z*: 340 M^+, 329, 266, 222, 187, 129, 85, 55. Anal. calcd for $C_{16}H_{22}BrNO_2$ (340.25): C, 56.48%; H, 6.52%; Br, 23.48%; N, 4.12%. Found: C, 56.5%; H, 6.55%; Br, 23.5%; N, 4.14%.

Compound **2g**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J=2.6 Hz, 1H, H_3), 7.04 (dd, J=2.6, 8.0 Hz, 1H, H_2), 6.38 (d, J=8.0 Hz, 1H, H_1), 4.98 (d, J=5.5 Hz, 1H, H_4), 3.62 (m, 2H, H_{10} and $H_{10'}$), 3.60 (m, 1H, H_{13}), 3.42 (m, 1H, $H_{13'}$), 3.36 (m, 1H, H_6), 2.0 (m, 1H, H_5), 1.70–1.32 (m, 10H).

Compound **3g**: *exo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, J=2.6 Hz, 1H, H_3), 7.10 (dd, J=2.6, 8.0 Hz, 1H, H_2), 6.40 (d, J=8.0 Hz, 1H, H_1), 4.40 (d, J=3.0 Hz, 1H, H_4), 3.86 (m, 1H), 3.65 (m, 3H), 3.46 (m, 1H), 1.84 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.8. R=*o*,*m*-Difluoro, 4-(7,9-difluoro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2h, 3h). Solid, mp 91–92°C. IR (KBr): ν_{max}: 3395, 2935, 2845, 1575, 1470, 1260, 1070, 810, 755. EIMS: *m*/*z*: 297 M^+, 224, 180, 166. Anal. calcd for $C_{16}H_{21}F_2NO_2$ (297.34): C, 64.63%; H, 7.12%; F, 12.78%; N, 4.71%. Found: C, 64.65%; H, 7.15%; F, 12.8%; N, 4.75%.

Compound **2h**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (s, 1H, H_1), 6.68 (s, 1H, H_2), 5.00 (d, J=5.7 Hz, 1H, H_3), 3.66 (t, J=6.3 Hz, 2H, H_9 and $H_{9'}$), 3.56 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{12}), 3.32 (dt, J=2.3, 11.4 Hz, 1H, $H_{12'}$), 3.31 (dt, J=2.2, 7.0 Hz, 1H, H_5), 2.08 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_4), 1.70–1.32 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 148.0, 108.90, 108.60, 103.6, 103.3, 102.70, 102.21, 72.03, 62.53, 61.06, 54.07, 35.30, 32.55, 31.83, 25.18, 22.12, 17.87.

4.1.9. R=*m*-NO_2, 4-(8-Nitro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-5-yl)-1-butanol (2i, 3i). Viscous oil. IR (KBr): ν_{max}: 3410, 2950, 2860, 1630, 1515, 1365, 1320, 1145, 807, 757. EIMS: *m*/*z*: 306 M^+, 247, 238, 189, 130. Anal. calcd for $C_{16}H_{22}N_2O_4$ (306.35): C, 62.73%; H, 7.24%; N, 9.14%. Found: C, 62.76%; H, 7.28%; N, 9.16%.

Compound **2i**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (s, 1H, H_3), 6.82 (d, J=8.0 Hz, 1H, H_2), 6.62 (d, J=8.0 Hz, 1H, H_1), 5.38 (d, J=5.8 Hz, 1H, H_4), 3.68 (t, J=6.3 Hz, 2H, H_{10} and $H_{10'}$), 3.54 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{13}), 3.32 (dt, J=2.3, 11.4 Hz, 1H, $H_{13'}$), 3.10 (dt, J=2.6, 7.3 Hz, 1H, H_6), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 151.40, 146.05, 128.87, 118.54, 112.63, 112.55, 69.26, 62.26, 61.96, 53.62, 34.14, 32.32, 24.52, 23.72, 20.83, 17.81.

Compound **3i**: *exo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (s, 1H, H_3), 7.00 (d, J=8.0 Hz, 1H, H_2), 6.70 (d, J=8.0 Hz, 1H, H_1), 4.98 (d, J=5.8 Hz, 1H, H_4), 3.88 (m, 1H), 3.68 (m, 3H), 3.36 (m, 1H), 1.82 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.10. R=*p*-CH_2CN, 2-[5-(4-Hydroxybutyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-9-yl]-acetonitrile (2j, 3j). Solid, mp 58–59°C. IR (KBr): ν_{max}: 3365, 2934, 2862, 1619, 1506, 1461, 1304, 1069, 812, 755. EIMS: *m*/*z*: 300 M^+, 227, 183, 169. Anal calcd for $C_{18}H_{24}N_2O_2$ (300.39): C, 71.97%; H, 8.05%; N, 9.33%. Found: C, 71.99%; H, 8.09%; N, 9.36%.

Compound **2j**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, H_3), 6.98 (d, J=7.5 Hz, 1H, H_2), 6.42 (d, J=7.5 Hz, 1H, H_1), 4.98 (d, J=5.6 Hz, 1H, H_4), 3.62 (t, J=6.3 Hz, 2H, H_{11} and $H_{11'}$), 3.60 (m, 2H, H_7), 3.58 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{14}), 3.38 (dt, J=2.3, 11.4 Hz, 1H, $H_{14'}$), 3.32 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.00 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled): δ 144.75, 127.44, 127.04, 120.40, 118.37, 114.22, 72.03, 62.24, 60.66, 53.91, 35.08, 32.40, 31.69, 25.20, 22.82, 22.57, 22.00, 17.73.

4.1.11. R=*o*-CN, 5-(4-Hydroxybutyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-7-yl cyanide (2k, 3k). Viscous oil. IR (KBr): ν_{max}: 3385, 2933, 2862, 2220, 1573, 1458, 1336, 1039, 805, 755. EIMS: *m*/*z*: 286 M^+, 214, 169, 117, 71, 41. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30%; H, 7.74%; N, 9.78%. Found: C, 71.33%; H, 7.76%; N, 9.82%.

Compound **2k**: *endo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J=7.8 Hz, 1H, H_3), 7.24 (d, J=7.8 Hz, 1H, H_1), 6.60 (t, J=7.8 Hz, 1H, H_2), 4.98 (d, J=5.7 Hz, 1H, H_4), 3.68 (m, 2H, H_{10} and $H_{10'}$), 3.58 (m, 1H, H_{13}), 3.48 (m, 1H, $H_{13'}$), 3.28 (m, 1H, H_6), 2.00 (m, 1H, H_5), 1.70–1.32 (m, 10H).

Compound **3k**: *exo*-isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J=7.8 Hz, 1H, H_3), 7.28 (d, J=7.8 Hz, 1H, H_1), 6.65 (t, J=7.8 Hz, 1H, H_2), 4.42 (d, J=5.7 Hz, 1H, H_4), 3.80 (m, 1H), 3.68 (m, 3H), 3.45 (m, 1H), 1.80 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.12. R=*p*-CN, 5-(4-Hydroxybutyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinolin-9-yl cyanide(2l, 3l). Solid, mp 68–70°C. IR (KBr): ν_{max}: 3365, 2935, 2860,

2135, 1600, 1500, 1305, 1070, 807, 745. EIMS: *m*/*z*: 286 M^+, 213, 169, 84, 48. Anal calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30%; H, 7.74%; N, 9.78%. Found: C, 71.33%; H, 7.78%; N, 9.80%.

Compound **2l**: *endo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J=2.2 Hz, 1H, H_3), 7.24 (dd, J=2.2, 8.0 Hz, 1H, H_2), 6.44 (d, J=8.0 Hz, 1H, H_1),4.98 (d, J=5.7 Hz, 1H, H_4), 4.25 (brs, NH),3.64 (t, J=6.3 Hz, 2H, H_{10} and $H_{10'}$), 3.58 (ddt, J=1.6, 4.4, 11.4 Hz, 1H, H_{13}), 3.42 (dt, J=2.3, 11.4 Hz, 1H, $H_{13'}$), 3.36 (dt, J=2.2, 7.0 Hz, 1H, H_6), 2.02 (dddd, J=3.0, 5.4, 7.1, 12.1 Hz, 1H, H_5), 1.70–1.32 (m, 10H).

Compound **3l**: *exo*-isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J=1.8 Hz, 1H, H_3), 7.26 (dd, J=1.8, 8.0 Hz, 1H, H_2), 6.44 (d, J=8.0 Hz, 1H, H_1), 4.65 (brs, NH), 4.44 (d, J=3.0 Hz, 1H, H_4), 3.85 (m, 1H), 3.68 (m, 3H), 3.42 (m, 1H), 1.85 (m, 1H, H_5), 1.70–1.32 (m, 10H).

4.1.13. R=1-Naphthyl, 4-(2,3,4a,11,12,12a-hexahydro-1*H*-benzo[*h*]pyrano[3,2-*c*]quinolin-12-yl)-1-butanol (2m, 3m). Compound **2m**: *endo*-isomer, viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 2H, H_3 and H_2), 7.48 (d, J=8.0 Hz, 1H, H_5), 7.38 (m, 2H, H_1 and H_4), 7.22 (d, J=8.0 Hz, 1H, H_6), 5.20 (d, J=5.6 Hz, 1H, H_7), 3.70 (m, 2H, H_{13} and $H_{13'}$), 3.60 (m, 1H, H_{16}), 3.42 (m, 1H, $H_{16'}$), 3.32 (m, 1H, H_6), 2.08 (m, 1H, H_8), 1.70–1.32 (m, 10H). IR (KBr): ν_{max}: 3396, 2934, 2861, 1575, 1521, 1469, 1212, 1079, 1032, 807, 759. EIMS: *m*/*z*: 311 M^+, 238, 207, 180, 41. Anal calcd for $C_{20}H_{26}NO_2$ (311.42): C, 77.14%; H, 8.09%; N, 4.50%. Found: C, 77.18%; H, 8.12%; N, 4.53%.

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