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INTRAMOLECULAR AMINOLYSIS OF 2'-AMINOCHALCONE EPOXIDES USING InBr₃ OR BiCl₃ AS EFFICIENT CATALYSTS

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GRAPHICAL ABSTRACT



Abstract In the synthesis of aza-flavanone derivatives, several metal halides were screened for their catalytic activity. Among them, BiCl₃ and InBr₃ catalyze the ring opening of 2'-aminochalcone epoxides followed by intramolecular aminolysis under mild conditions. The reactions proceed efficiently at room temperature to afford highly functionalized 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones (aza-flavanones) in excellent yields (82– 92%). Intermolecular aminolysis of 2'-aminochalcone epoxides with aniline derivatives failed under the same catalytic conditions.

Keywords 2'-Aminochalcones/epoxides; aminolysis; 2-aryl-3-hydroxy-2,3-dihydro-4quinolones; epoxide ring opening; metal halides

INTRODUCTION

2-Aryl-2,3-dihydro-4-quinolones (aza-flavanones) are common structural intermediates in the biogenesis of naturally occurring flavonoid-type derivatives and are widely used for the synthesis of medicinal compounds.^[1] Derivatives of 2-aryl-4-quinolones and 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones displayed interesting biological properties,^[2] such as cytotoxicity against human tumor cell lines,^[3] anticancer activity in the xenograft ovarian OVCAR-3 model, 13% increase in life span mice,^[4] tubulin polymerization inhibition,^[5] colchicines binding to tubulin,^[6] hepatoprotective activity, ^[7] and potential use as scintillator dyes in photo-oxidative stability.

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Scheme 1. Optimization reaction in synthesis of flavonols.

Different synthetic strategies have been reported for the substituted azaflavanones.^[1,2] Among them, the Alger–Flynn–Oyamada (AFO) reaction is the most common approach,^[8] in which the treatment of 2'-aminochalcones with alkaline H₂O₂ at high temperature afforded flavonol and aurone as major and minor products, respectively. In this reaction, the substitution patterns on aromatic rings influence the rate of the reaction; for example, some substitution patterns of methoxy group on the aromatic rings gave aurone as major product [9-11] and incorporation of electron-withdrawing groups at C-4 required longer reaction time.^[12] Similarly, elevated temperature and strong alkaline conditions are other drawbacks for many functional groups present in the molecule. Thus, the product ratio in the AFO reaction depends on the nature of substituents as electron donating or withdrawing and their substitution pattern on the aromatic rings. Mechanistically, the AFO reaction follows epoxide intermediate formation.^[12–15] Therefore, this reaction is not the right choice for stereoselectivity toward flavonols. To improve regioselectivity and yields toward flavonol derivatives, different protic acids were used either as catalyst or promoter, including concentrated HCl, H₂SO₄, CF₃COOH, and AcOH.^[16,17] These catalysts or promoters have been used efficiently in many cases. However, the use of strong acids, high temperature, and prolonged reaction time are major drawbacks, and the stereoselectivity toward flavonol or aurone remains unresolved. To address these environmental concerns in chemical synthesis and stereoselectivity calls for clean and efficient catalytic procedures that can avoid use of harmful catalysts.

In continuation of our interest in Lewis acid catalysis^[18–23] and the importance of metal halides as inexpensive, easily available, and stable catalysts in epoxide ring opening,^[24–29] we report the catalytic properties of various metal salts. Among them, InBr₃ and BiCl₃ were found to be excellent catalysts under mild conditions (Scheme 1, Table 1). The reaction proceeded efficiently at room temperature to afford highly functionalized 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones in excellent yield (82–92%). However, intermolecular aminolysis of 2'-aminochalcone epoxides with aniline derivatives failed under same catalytic conditions. In comparison with other methods, our method gave good yields in shorter reaction time with easy work-up.

RESULTS AND DISCUSSION

The catalytic efficiency of metal salts is given in Table 1. Entries 1 and 2 ($InBr_3$ and $BiCl_3$) were the most efficient catalysts, which gave optimal yields (92 and 90%, respectively) at 10 mol% catalyst loading (Tables 1 and 2). Entries 3–10 at 10 mol%

AMINOLYSIS OF 2'-AMINOCHALCONE EPOXIDES

| Entry | Metal salt | Time (min) | Yield (%) ^b | |
|-------|--------------------------------------|------------|------------------------|--|
| 1 | InBr ₃ | 45 | 92 | |
| 2 | BiCl ₃ | 50 | 90 | |
| 3 | MgI ₂ | 70 | 60 | |
| 4 | TaBr ₅ | 40 | 70 | |
| 5 | NbCl ₅ | 60 | 50 | |
| 6 | ZrCl ₄ | 70 | 50 | |
| 7 | $ZnCl_2$ | 55 | 55 | |
| 8 | InCl ₃ | 50 | 80 | |
| 9 | Anhyd. AlCl ₃ | 45 | 65 | |
| 10 | AlCl ₃ ·6H ₂ O | 65 | 40 | |

Table 1. Screening of metal salts^a for the aminolysis of 2'-aminochalcone epoxides

^{*a*}GaCl₃, SnCl₂, ZnO, CuBr₂, CeCl₃·7H₂O, TeCl₄, LaCl₃, LiBr, AuBr₃, and MgBr₂·Et₂O failed to give products even for longer reaction time.

^bYields refer to isolated products **1b** in 10 mol% catalyst loading.

catalyst loading gave moderate to good yields (40-70%) along with corresponding halides (5-10%) as minor products at the C-3 position except for entries 1, 2, and 3 (Table 1). Further increase in catalyst loading gave more side product without improving the desired product. Some metal salts Listed in the footnote to Table 1 failed to catalyze the reaction even with longer reaction times.

Catalyst optimization is also reported for the most efficient catalyst, InBr₃, in Table 2 for Scheme 1. To optimize the catalyst loading, the reactions were carried out in 2, 5, 10, and 20 mol% catalyst loadings in dichloromethane at room temperature, and the efficiency of the catalyst loading was determined from the time needed for the complete conversion of epoxide. Reactions with InBr₃ at 2 and 5 mol% catalyst loading proceeded slowly (2–3 h), whereas at 20 mol% catalyst loading gave the product along with minor product as 3-bromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one (7%), which was isolated and characterized by gas chromatography–mass Spectrometry (GCMS) analysis.

2'-Aminochalcones were prepared from 2'-aminoacetophenones and aromatic aldehydes following the reported procedure.^[14] Epoxidation of 2'-aminochalcones was carried out with NaOH and H₂O₂ (30%, wt%) in aqueous tetrahydrofuran (THF) to afford epoxides in good yields (80–90%) (see the experimental section).

Following a simple experimental procedure, three different types of substituted 2'-aminochalcone epoxides (1a-8a, 9a-11a and 12a-16a) were dissolved in dichloromethane by stirring, and InBr₃ was added in portions and stirred at room

| Entry | Catalyst loading (mol%) | Time (h) | Yield (%) | | | | |
|-------|-------------------------|----------|--------------|--|--|--|--|
| 1 | 2 | 10 | 55 | | | | |
| 2 | 5 | 7 | 65 | | | | |
| 3 | 10 | 0.7-0.8 | 92 | | | | |
| 4 | 20 | 2–3 | $80 + 7^{a}$ | | | | |
| • | 20 | 2 5 | 00 1 | | | | |

Table 2. Optimization of InBr3 catalyst in Scheme 1

^aSide product 3-bromo-2-phenyl-2,3-dihydroquinolin-4(1H)-one (7%).

temperature for 45–50 min. After usual workup, 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones **1b–16b** was obtained in 82–92% yields (Scheme 2, Table 3).

The assigned structures of 2'-aminochalcone epoxides **1a–16a** and products **1b– 16b** were confirmed on the basis of their spectral analysis [infrared (IR), ¹H and ¹³CNMR, and GC-MS/HRMS]. The products were further compared with available data in the literature.^[30] The *trans*-stereochemistry of epoxides 1a-16a was confirmed by the coupling constants of the α - and β -protons. For example, **3a**, in the ¹H NMR (500 MHz) data [δ (ppm): 4.23 (d, J = 2.0 Hz, β -H, 1H), 4.03 (d, J = 2.0 Hz, α -H, 1H)], the J values (2 Hz) indicate a trans-substituted epoxide. The cis-configuration of 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones 1b-16b was confirmed by the coupling constants of their α - and β -protons. For example, **3b**, in the ¹H NMR data $[(500 \text{ MHz}) \delta \text{ (ppm)}: 5.26 \text{ (d, } J = 3.0 \text{ Hz}, \beta \text{-H}, 1 \text{H}), 5.51 \text{ (d, } J = 3.0 \text{ Hz}, \alpha \text{-H}, 1 \text{H})],$ the J values (3 Hz) indicate a *cis*-configuration. Similarly, substituted 3-hydroxy-1acetyl-2,3-dihydroquinolin-4(1H)-ones, for example, 14b, were also comfirmed on the basis of ¹H NMR data for their *cis*-configuration (Table 4, Fig. 1). 2'-Amino and 2'-amide chalcones were followed the plausible reaction path as shown in Scheme 3. The enhanced stereoselectivity and good yield for flavonols under acidic conditions might be due to the β -carbon possessing considerable cationic character at the benzylic position and therefore being resonance stabilized. The cisconfiguration in 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones further support benzylic resonance stabilization, which results in a S_N1-like mechanism instead of a S_N2-type mechanism in basic conditions (Scheme 3).

We also subjected 2'-hydroxychalcone epoxide analogs to the same reaction conditions which resulted in poor yields (10–20%) even after 2–5 h. This lack of reactivity might be due to the low nucleophilicity of oxygen in 2'-hydroxychalcone epoxides as compared to the amino nitrogen in 2'-aminochalcone epoxides. To establish broader catalytic efficiency in the synthesis of aza-flavanones, primary and secondary amines were also tested for their nucleophilicity. The yields were not very



Scheme 2. Inter- and intramolecular aminolysis of chalcone epoxides.

AMINOLYSIS OF 2'-AMINOCHALCONE EPOXIDES



Table 3. Intramolecular aminolysis of 2'-aminochalcone epoxides

(Continued)



Table 3. Continued

(Continued)



Table 3. Continued

^aAll reactions were carried out according to the general procedure.

^bReaction time: 45–50 min at room temp. in all entries.

^cYields refer to isolated products with InBr₃ catalyst (10 mol%).

different in both cases; however, primary amines were better nucleophiles than secondary amines **12b–16b**, perhaps due to steric and electronic factors (Table 3).

Under a solid-supported reaction, 2'-aminochalcone epoxides and 2'-hydroxychalcone epoxides were adsorbed on solid-supported catalysts ($InBr_3$ -silica gel and $BiCl_3$ -silica gel) and stirred at room temperature to elevated temperature, but failed to give the flavonols.

Similarly, the intermolecular epoxide ring-opening reactions were shown with aniline derivatives under these catalytic conditions, which failed to give the product **17** (Scheme 2).

| ¹ H- | 3b (δ, ppm) | $^{1}\mathrm{H}$ | 14b (δ, ppm) | ¹³ C | 3b (δ, ppm) | 14b (δ, ppm) |
|---------------------------------------|---|-------------------|--------------------------------------|--------------------|-----------------------|------------------------|
| -NH | 6.31 (s, br, D ₂ O- exchangeable) | | _ | | _ | |
| 2 | 5.26 (d, $J = 3.0$ Hz, 1H) | 2 | 5.07 (d, $J = 4.0$ Hz, 1H) | 2 | 63.05 | 58.25 |
| 3 | 5.51 (d, $J = 3.0$ Hz, 1H) | 3 | 5.31 (d, $J = 4.5$ Hz, 1H) | 3 | 76.11 | 75.03 |
| -OH | 3.70 (s, br, D_2O - exchangeable) | Ar-5 | 8.31 (d, $J_1 = 8.0$ Hz, 1H) | 4 | 197.18 | 198.28 |
| Ar-5,6,7,8 and Ar'- 2',3',4',5' | 6.70–7.67(m, 8H) | Ar-6,8 | 7.22 (m, 2H) | Ar 5 | 126.32 | 128.55 |
| | | Ar-7 | 7.58 (m, 1H) | Ar 6 | 116.03 | 119.26 |
| | | -OH | 3.89 (s, br, D_2O - exchngeble) | Ar 7 | 130.98 | 131.20 |
| | | -CH ₃ | 2.15 (s, 3H) | Ar 8 | 117.15 | 115.59 |
| | | -OCH ₃ | 3.45 (s, 3H) | Ar-C | 151.00 | 151.71 |
| | | Ar'-2',6' | 7.32 (m, 2H) | Ar-C | 122.94 | 117.49 |
| | | Ar'-3',5' | 7.41 (m, 2H) | -COCH ₃ | | 168.92 |
| | | | | -CH ₃ | | 23.96 |
| | | | | -OCH ₃ | | 61.05 |
| | | | | Ar'1' | 136.20 | 135.78 |
| | | | | Ar'2',6' | 128.74 | 127.45 |
| | | | | Ar'3',5' | 129.11 | 115.24 |
| | | | | Ar'4' | 128.06 | 159.18 |

Table 4. ¹H and ¹³C NMR data for compounds 3b and 14b

CONCLUSION

In conclusion, we have reported the catalytic properties of metal halides in the synthesis of 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones. BiCl₃ and InBr₃ were explored as mild and efficient catalysts for the regioselective ring opening and intramolecular aminolysis of 2'-aminochalcone epoxides at room temperature. To the best of our knowledge, InBr₃ and BiCl₃ had not been studied in this capacity before and therefore are novel subjects for investigation.



Figure 1. Protected and unprotected 3-hydroxy-dihydroquinolines of 3b and 14b.



Scheme 3. Plausible mechanism with InBr₃(10 mol%).

EXPERIMENTAL

Organic solvents were dried by standard methods when necessary. Commercially available reagents were used without further purification unless mentioned. Aniline was freshly distilled under reduced pressure prior to use. All reactions were monitored by thin-layer chromatography (TLC) using precoated silica-gel aluminum plates. Visualization of TLC plates was accomplished with ultraviolet (UV) lamp or in an iodine chamber. Column chromatography was performed using silica gel (100–200 mesh) (SD Fine-Chem Limited) with ethyl acetate / hexanes as an eluent system. Melting points were recorded on Perfit apparatus and are uncorrected. The IR spectrum was recorded with KBr on a Thomso Nicolet Fourier transform (FT)-IR spectrophotometer. IR spectra of the compounds were expressed as wave numbers (cm⁻¹). ¹H and ¹³C NMR spectra were obtained in CDCl₃ on a Bruker Spectrospin-500/125 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts of ¹H NMR spectra were given in parts per million with respect to TMS, and the coupling constant J was measured in hertz (Hz). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, br = broad). Mass spectra were recorded on Perkin-Elmer Clarus-500 instrument (EI, 70 eV) as GC-MS. HR-MS spectra were recorded on Bruker instruments.

General Procedure: Synthesis of 2'-Aminochalcone Epoxides

Aqueous NaOH (5 M, 10 ml) was added dropwise to a stirred solution of 2'-aminochalcones (18 mmol) in aqueous THF (30 ml, H_2O -THF, 1:2 ratio) and further stirred for 10 min. Then, H_2O_2 (15 ml, 30% wt%) was added dropwise and further stirred for 6–7 h at room temperature. With TLC monitoring, the reaction mixture was poured in H_2O . The resulting precipitate was filtered, washed with water, and dried under reduced pressure. The product was recrystallized in EtOH or silica-gel column chromatography in petroleum ether–CH₂Cl₂ as eluent to give the products in 80–90% yield.

Selected Spectral Data

(2-Aminophenyl)(3-(4-chlorophenyl)oxiran-2-yl)methanone 3a (Table 2). Yield: 88%. White solid, mp: 120–125 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.70–7.69 (dd, $J_1 = 1.5$ Hz, $J_2 = 1.0$ Hz, 1H), 7.38–7.36 (m, 2H), 7.33–7.29 (m, 3H), 6.71–6.69 (dd, $J_1 = 1.5$ Hz, $J_2 = 1.0$ Hz, 1H), 6.65–6.61 (m, 1H), 6.33 (s, br, D₂O exchangeable), 4.23 (d, J = 2 Hz, 1H), 4.03 (d, J = 2 Hz, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 193, 151, 135.36 135, 134, 130, 129, 127, 117, 116.74, 116, 61, 58. IR (KBr) cm⁻¹: 3443, 3321, 1640, 1545, 1483, 1228, 1161, 1087, 1017, 901, 807, 752, 648. GC-MS (m/z): 273 [M⁺⁻, C₁₅H₁₂ClNO₂], 257, 244, 220, 207, 165, 145, 132 (100), 120, 105, 91, 77, 65.

(2-Aminophenyl)-3-(4-bromophenyl-oxiran-2-yl)methanone 4a (Table 2). Yield: 86%. White solid, mp: 130–134 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.69–7.67 (dd, $J_1 = 3.5$ Hz, $J_2 = 4.5$ Hz, 1H), 7.53–7.52 (m, 1H), 7.32–7.29 (m, 1H), 7.25 (dd, $J_1 = 2.0$ Hz, $J_2 = 4.5$ Hz, 3H), 6.70–6.68 (dd, $J_1 = 1.0$ Hz, $J_2 = 0.5$ Hz, 1H), 6.64–6.61 (m, 1H), 6.33 (s, br, D₂O exchangeable), 4.23 (d, J = 1.5 Hz, 1H), 4.00 (d, J = 2.0 Hz, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 192.95, 150.85, 135.39, 134.90, 132.02, 131.96, 130.37, 122.95, 117.42, 116.69, 116.15, 60.92, 58.48. IR (KBr) cm⁻¹: 3445.44, 3321.68, 1642.48, 1547.33, 1393.34, 1228.51, 1160.11, 1067.15, 899.62, 800.22, 751.78, 659.71. GC-MS (m/z): 317 [M⁺⁻, C₁₅H₁₂BrNO₂], 300, 288, 264, 219, 146, 132(100), 125, 120, 91, 77, 65.

(2-Amino-5-bromo-phenyl)-(3-phenyl-oxiranyl)-methanone 9a (Table 2). Yield: 82%. ¹H NMR (CDCl₃, 500 MHz): δ 7.72 (d, $J_1 = 1.5$ Hz, 1H), 7.34–7.38 (m, 5H), 7.21–7.19 (dd, $J_1 = 2.0$, $J_2 = 1.5$, 1H), 6.59 (d, 1H), 6.32 (s, br, D₂O exchangeable), 4.32 (d, J = 2 Hz, 1H), 4.10 (d, J = 2 Hz, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 193.11, 149.82, 138.84, 135.27, 130.49, 129.95, 128.78, 125.85, 118.39, 116.80, 114.08, 61.62, 59.51. IR (KBr) cm⁻¹: 3445.37, 3325.03, 1640.76, 1500.48, 1218.79, 1158.54, 1020.35, 890.16, 801.67, 746.75, 694.39, 654.37. GC-MS (m/z): 318 [M⁺⁻, C₁₅H₁₂BrNO₂].

(2-Amino-5-bromo-phenyl)-[3-(4-fluoro-phenyl)-oxiranyl]-methanone 10a (Table 2). Yield 85%. White solid, mp: 120–123 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.69 (d, J=1.5 Hz, 1H), 7.53–7.52 (dd, J_1 =1.5, J_2 =1.0, 1H), 7.32 (d, 2H), 7.25 (d, 2H), 6.70 (d, 1H), 6.33 (s, br, D₂O exchangeable), 4.22 (d, J=1.5 Hz, 1H), 4.09 (d, J=2.0 Hz, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 192.95, 150.85, 135.39, 134.90, 132.02, 131.96, 130.37, 122.95, 117.42, 116.69, 116.15, 60.92, 58.48. IR (KBr) cm⁻¹: 3448.44, 3325.68, 1640.48, 1549.30, 1392.35, 1223.55, 1165.11, 1065.15, 898.62, 800.22, 751, 659. HR-MS (m/z): 335 [M⁺⁻, C₁₅H₁₁BrFNO₂].

2-(N-Acetylaminophenyl)-3-phenyl-oxiran-2-yl-methanone 12a (Table 2). White solid. Yield: 69%. ¹H NMR (CDCl₃, 500 MHz): δ 11.36 (s, br, D₂O exchangeable 1H), 8.56 (d, $J_1 = 8.0$ Hz, 1H), 7.81 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, 1H), 7.62 (m, 1H), 7.57 (m, 3H), 7.28 (m, 3H), 4.30 (d, J = 2.0 Hz, 1H), 4.06 (d, J = 2.0 Hz, 1H), 2.26 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 194.51, 168.95, 149.95, 135.97, 134.05, 131.99, 129.85, 127.05, 123.09, 122.31, 121.05, 120.56, 61.35, 59.12, 25.49. IR (KBr) cm⁻¹: 3359, 3078, 1669, 1639, 1582, 1411, 1356, 1233, 754. GC-MS (m/z): 281 [M^{+,}, C₁₇H₁₅NO₃].

2-(N-Acetylaminophenyl)-3-(4-methoxyphenyl)-oxiran-2-yl-methanone 14a (Table 2). White solid. Yield: 61%. ¹H NMR (CDCl₃, 500 MHz): δ 11.31 (s, br, D₂O exchangeable 1H), 8.75 (d, $J_1 = 8.0$ Hz, 1H), 7.77 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, 1H), 7.55 (m, 1H), 7.41 (m, 1H), 7.21 (m, 4H), 4.29 (d, J = 2.0 Hz, 1H), 4.07 (d, J = 2.0 Hz, 1H), 3.49 (s, 3H) 2.22 (s, CH₃). ¹³C NMR (CDCl₃, 125 MHz): δ 195.46, 169.84, 159.11, 140.45, 134.21, 133.51, 132.38, 127.90, 126.29, 124.07, 123.16, 121.41, 75.64, 61.93, 59.25, 24.04. IR (KBr) cm⁻¹: 3345, 3025, 2928, 1682, 1630, 1591, 1459, 1399, 1233, 1130, 1007, 823. GC-MS (m/z): 311 [M⁺, C₁₈H₁₇NO₄].

General Procedure: Synthesis of 3-Hydroxy-aza-flavonone Derivatives

2'-Aminochalcone epoxides (2.5 mmol) were dissolved in dichloromethane (10 mL) by stirring, and indium bromide (0.25 mmol, 10 mol%) was added in portions and stirred for 45–50 min at room temperature. The reaction mixture was extracted with CH_2Cl_2 by adding water. The organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated under reduced pressure to obtain the pure product or purified by flash column chromatography on silica gel using hexane– CH_2Cl_2 (8:2) as eluent to afford the products.

Selected Spectral Data

cis-3-Hydroxy-2-phenyl-2,3-dihydroquinolin-4(1H)-one 1b (Table 2). Yields: 92%. ¹H NMR (CDCl₃, 500 MHz): δ 3.67 (s, br, D₂O-exchangeable), 5.10 (d, J = 5 Hz, 1H), 5.38 (d, J = 5 Hz, 1H), 6.33 (s, br, D₂O-exchangeable), 6.72–7.71 (m, 9H). ¹³C NMR (CDCl₃, 125 MHz): δ 196.48, 152.42, 137.90, 135.07, 133.75, 128.85, 127.77, 126.96, 126.63, 123.75, 119.28, 74.52, 63.43. IR (KBr) cm⁻¹: 3480.11, 3350.11, 1675.55, 1617.55, 1479.79, 1369.59, 1310.63, 1253.61, 1102.28, 974.42, 754.17, 701.16. GC-MS (m/z): 239 [M^{+,} C₁₅H₁₃NO₂]: 220, 190, 148 (100), 130, 120, 91, 77, 65, 51. HR-MS (m/z) for C₁₅H₁₃NO₂ calcd. 239.0946; found: 239.0940. GC purity: 94%.

cis-3-Hydroxy-2-p-tolyl-2,3-dihydroquinolin-4(1H)-one 2b (Table 2). Yields: 88%. ¹H NMR (CDCl₃, 500 MHz): δ 2.45 (s, 3H), 3.70 (s, br, D₂O-exchangeable), 5.25 (d, J= 3 Hz, 1H), 5.50 (d, J= 3 Hz, 1H), 6.32 (s, br, D₂O-exchangeable), 6.52–7.7 (m, 8H). ¹³C NMR (CDCl₃, 125 MHz): δ 197, 152, 136, 132, 129, 128.74, 128.27, 126.15, 123.61, 117.60, 116.40, 76.03, 62.92, 22.06. IR (KBr) cm⁻¹: 3478.01, 3359.15, 2922.44, 1687.08, 1611.14, 1488.32, 1407.29, 1311.25, 1260.80, 1160.45, 1094.38, 1016.09, 973.8, 752.56. GC-MS (*m*/*z*): 253 [M^{+,} C₁₆H₁₅NO₂]; 254, 193, 165, 148(100), 125, 119, 91, 77, 65, 51. HR-MS (*m*/*z*) for C₁₆H₁₅NO₂ calcd. 253.1103; found: 253.1092. GC purity: 90%.

cis-2-4-Chlorophenyl-3-hydroxy-2,3-dihydroquinolin-4(1H)-one 3b (Table 2). Yield: 90%. ¹H NMR (CDCl₃, 500 MHz): δ 3.70 (s, br, D₂O-exchangeable), 5.26 (d, J = 3 Hz, 1H), 5.51 (d, J = 3 Hz, 1H), 6.31 (s, br,

D₂O-exchangeable), 6.70–7.67 (m, 8H). ¹³C NMR (CDCl₃, 125 MHz): δ 197, 151, 136, 131, 129, 128.74, 128, 126, 123, 117, 116, 76, 63. IR (KBr) cm⁻¹: 3478, 3359, 2922, 1687, 1611, 1488, 1407, 1311, 1261, 1160, 1094, 1016, 974, 752. GC-MS (m/z): 273 [M^{+,} C₁₅H₁₂ClNO₂], 257, 254, 193, 165, 148 (100), 125, 119, 91, 77, 65, 51. HR-MS (m/z) for C₁₅H₁₂ClNO₂ calcd. 273.0557; found: 273.0550. GC purity: 92%.

cis-2-(4-Bromophenyl)-3-hydroxy-2,3-dihydroquinolin-4(1H)-one 4b (Table 2). Yield: 92%.¹H NMR (CDCl₃, 500 MHz): δ 4.51 (s, br, D₂O-exchangeable), 5.25 (d, J = 3 Hz, 1H), 5.51 (d, J = 3.5 Hz, 1H), 6.34 (s, br, D₂O-exchangeable), 6.71–7.67 (m, 8H). ¹³CNMR (CDCl₃, 125 MHz): δ 196.7, 151.18, 132.37, 131.91, 130.28, 129.46, 125.69, 122.89, 120.91, 115.81, 114.38, 75.96, 62.45. IR (KBr) cm⁻¹: 3480.53, 3359.30, 2921.87, 1687.58, 1484.38, 1408.10, 1313.71, 1257.51, 1099.52, 1072.58, 1009.65, 749.24 and 702.48. GC-MS (*m*/*z*): 317 [M⁺, C₁₅H₁₂BrNO₂], 196, 139, 105, 91, 77, 65, 51. HRMS (*m*/*z*) for C₁₅H₁₂BrNO₂ calcd. 317.0051; found: 317.0042. GC purity: 93%.

cis-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one 5b (Table 2). Yields: 85%.¹H NMR (CDCl₃, 500 MHz): δ 3.53 (s, 3H), 3.56 (s, br, D₂O-exchangeable), 4.48 (d, J=3.0 Hz, 1H), 4.81 (d, J=3.5 Hz, 1H), 6.26 (s, br, D₂O-exchangeable), 6.70–7.87 (m, 8H). ¹³CNMR (CDCl₃, 125 MHz): δ 198.9, 160.02, 151.51, 136.16, 130.30, 127.94, 127.85, 118.64, 116.35, 115.66, 114.30, 75.64, 64.17, 55.38. IR (KBr) cm⁻¹: 3480.11, 3350.30, 2924.02, 1665.22, 1610.08, 1512.69, 1478.26, 1400.03, 1248.49, 1177.61, 1095.47, 1026.09, 985.95, 755.09, 615.91. GC-MS (m/z): 269 [M⁺, C₁₆H₁₅NO₂]; 255, 208, 180, 165, 152, 148, 121(100), 106, 102, 91, 77, 65, 51. HR-MS (m/z) for C₁₆H₁₅NO₃ calcd. 269.1052; found: 269.1048. GC purity: 89%.

cis-6-Bromo-3-hydroxy-2-phenyl-2,3-dihydroquinolin-4(1H)-one 9b (Table 2). Yield: 82%. ¹H NMR (CDCl₃, 500 MHz): δ 3.82 (s, br D₂O-exchangeable), 5.02 (d, J = 5 Hz, 1H), 5.38 (d, J = 5.5 Hz, 1H), 6.30 (s, br, D₂O-exchangeable), 6.72–7.71 (m, 8H). ¹³CNMR (CDCl₃, 125 MHz): δ 197.48, 150.32, 137.90, 135.07, 128.95, 128.85, 127.97, 127.16, 126.63, 120.75, 119.28, 74.52, 63.43. IR (KBr): cm⁻¹ 3485.11, 3355.11, 1680.55, 1620.55, 1480.79, 1370.59, 1315.63, 1250.61, 1112.28, 979.42, 754.17, 701.16. GC-MS (m/z): 318 [M⁺⁻, C₁₅H₁₂BrNO₂]. HRMS (m/z) for C₁₅H₁₂BrNO₂ calcd. 317.0051; found: 317.0042. GC purity: 91%.

cis-6-Bromo-2-(4-fluorophenyl)-3-hydroxy-2,3-dihydroquinolin-4(1H)one 10b (Table 2). Yield: 85%. ¹H NMR (CDCl₃, 500 MHz): δ 3.75 (s, br, D₂Oexchangeable), 5.28 (d, J = 3 Hz, 1H), 5.50 (d, J = 3 Hz, 1H), 6.32 (s, br, D₂Oexchangeable), 6.70–7.66 (m, 7H). ¹³CNMR (CDCl₃, 125 MHz): δ 197.80, 160.11, 149.11, 138.94, 135.63, 130.38, 128.74, 128.27, 123.07, 117.60, 116.40, 75.89, 62.88. IR (KBr) cm⁻¹: 3479.01, 3350.15, 2911.44, 1690.08, 1619.14, 1485.32, 1412.29, 1318.25, 1256.80, 1167.45, 1099.38, 1019.09, 973.8, 760.56. GC-MS (*m*/*z*): 335 [M⁺, C₁₅H₁₁BrFNO₂]. HR-MS (*m*/*z*) for C₁₅H₁₁BrFNO₂ calcd. 334.9957; found: 334.9853. GC purity: 93%.

cis-6-Bromo-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1H)one 11b (Table 2). Yields: 85%. ¹H NMR (CDCl₃, 500 MHz): δ 3.69 (s, 3H), 3.89 (s, br, D₂O-exchangeable), 5.22 (d, J = 3.0 Hz, 1H), 5.43 (d, J = 3.5 Hz, 1H), 6.28 (s, br, D₂O-exchangeable), 6.70–7.87 (m, 7H). ¹³CNMR (CDCl₃, 125 MHz): δ 198.98, 159.02, 149.51, 136.16, 131.30, 127.94, 127.85, 119.64, 117.35, 115.66, 114.30, 75.64, 64.17, 55.38. IR (KBr) cm⁻¹: 3485.11, 3349.30, 2924.02, 1670.22, 1612.08, 1519.69, 1480.26, 1422.03, 1250.49, 1177.61, 1095.47, 1026.09, 985.95, 755.09, 615.91. GC-MS (*m*/*z*): 347 [M⁺⁺, C₁₆H₁₄BrNO₃]. HR-MS (*m*/*z*) for C₁₆H₁₄BrNO₃ calcd. 347.0157; found: 347.0150. GC purity: 92%.

cis-3-Hydroxy-1-acetyl-2-phenyl-2,3-dihydroquinolin-4(1H)-one 12b (Table 2). Yellowish solid. Yield: 90%. ¹H NMR (CDCl₃, 500 MHz): δ 8.10 (d, $J_1 = 8.0$ Hz, 1H), 7.61 (m, 2H), 7.45 (m, 2H), 7.32 (m, 2H), 7.19 (m, 2H) 5.36 (d, J = 5.0 Hz, 1H), 5.09 (d, J = 4.0 Hz, 1H), 3.90 (s, br, D₂O exchageble), 2.21 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 196.35, 169.94, 152.35, 137.87, 134.92, 133.68, 128.69, 127.65, 126.79, 126.49, 123.59, 119.17, 70.21, 55.94, 25.41. IR (KBr) cm⁻¹: 3305, 3071, 1662, 1621, 1585, 1407, 1351, 1245, 754. GC-MS (*m*/*z*): 281 [M⁺⁻, C₁₇H₁₅NO₃] 281. HR-MS (*m*/*z*) for C₁₇H₁₅NO₃ calcd. 281.1052; found: 281.1045. GC purity: 91%.

cis-2-(4-Bromophenyl)-3-hydroxy-1-acetyl-2,3-dihydroquinolin-4(1H)one 13b (Table 2). Yellow solid. Yield: 91%. ¹H NMR (CDCl₃, 500 MHz): δ 8.24 (d, $J_1 = 8.0$ Hz, 1H), 7.73 (m, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 7.24 (m, 2H), 5.46 (d, J = 5.0 Hz, 1H), 5.19 (d, J = 4.0 Hz, 1H), 4.13 (s, br, D₂O exchangeable), 2.19 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 197.92, 169.29, 151.05, 132.25, 131.85, 130.17, 129.39, 125.57, 122.81, 120.89, 115.76, 114.29, 69.15, 61.05, 25.48. IR (KBr) cm⁻¹: 3426, 2995, 2935, 1668, 1632, 1591, 1417, 1395, 1282, 1170, 1092, 650. GCMS (m/z): 359 [M⁺⁻, C₁₇H₁₄BrNO₃]. HR-MS (m/z) for C₁₇H₁₄BrNO₃ calcd. 359.0157; found: 359.0148. GC purity: 94%.

cis-2-(4-Methoxyphenyl)-3-hydroxy-1-acetyl-2,3-dihydroquinolin-4(1H)one 14b (Table 2). Yellowish solid. Yield: 83%. ¹H NMR (CDCl₃, 500 MHZ): δ 8.31 (d, $J_1 = 8.0$ Hz, 1H), 7.58 (m, 1H), 7.41 (m, 2H), 7.32 (m, 2H), 7.22 (m, 2H) 5.31 (d, J = 5.0 Hz, 1H), 5.07 (d, J = 4.0 Hz, 1H), 3.89 (s, br, D₂O exchangeble), 3.45 (s, 3H) 2.15 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 198.28, 168.92, 159.18, 151.71, 135.78, 131.20, 128.55, 127.45, 119.26, 117.49, 115.59, 115.24, 75.03, 61.05, 58.25, 23.96. IR (KBr): cm⁻¹ 3440, 2959, 2920, 1666, 1632, 1596, 1406, 1336, 1233, 1125, 1091, 771. GC-MS (*m*/*z*): 311 [M⁺⁺, C₁₈H₁₇NO₄]. HRMS (*m*/*z*) for C₁₈H₁₇NO₄ calcd. 311.1158; found: 311.1151. GC purity: 90%.

cis-2-(4-Chlorophenyl)-3-hydroxy-1-acetyl-2,3-dihydroquinolin-4(1H)one 16b (Table 2). Yellow solid. Yield: 92%. ¹H NMR (CDCl₃, 500 MHz): δ 8.21 (d, $J_1 = 8.0$ Hz, 1H), 7.69 (m, 1H), 7.50 (m, 2H), 7.39 (m, 2H), 7.25 (m, 2H) 5.39 (d, J = 5.0 Hz, 1H), 5.15 (d, J = 4.0 Hz, 1H), 4.01 (s, br, D₂O exchageble), 2.15 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 198.04, 170.10, 159.91, 136.15, 133.79, 132.95, 131.20, 130.85, 129.45, 126.92, 124.99, 123.55, 72.95, 59.89, 24.98. IR (KBr) cm⁻¹: 3338, 2922, 2895, 1665, 1627, 1591, 1395, 1281, 1171, 1089, 756. GCMS (*m*/*z*): 315 [M⁺⁺, C₁₇H₁₄ClNO₃]. HR-MS (*m*/*z*) for C₁₇H₁₄ClNO₃ calcd. 315.0662; found: 315.0655. GC purity: 95%.

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