

Synthesis of spiro(indoline-2,3'-hydropyridazine) *via* an “on-water”

[4 + 2] annulation reaction

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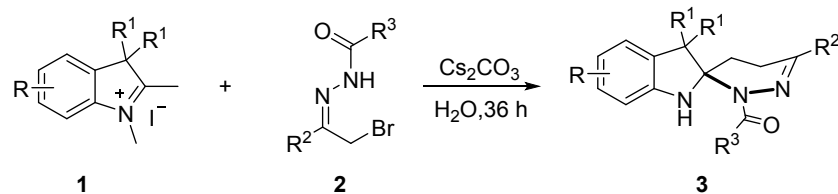
1. General methods

Nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ on Bruker 400, 600, 700 MHz, or JEOL 600 NMR instrument (at 400, 600 or 700 MHz for ¹H, and at 100, 150, or 175 MHz for ¹³C). The ¹H NMR chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as standard. The ¹³C NMR chemical shifts were given using CDCl₃ as the internal standard (CDCl₃: δ = 77.00 ppm). High-resolution mass spectra (HRMS) were obtained using Agilent P/N G1969-90010. High-resolution mass spectra were reported for the molecular ion [M+H]⁺ or [M+Na]⁺. Melting points were recorded on BUCHI Melting Point M-565 instrument. X-ray diffraction experiment was carried out on an Agilent Gemini and the data obtained were deposited at the Cambridge Crystallographic Data Centre. UV detection was performed at 254 nm. TLC was performed on glass-backed silica plates; products were visualized using UV light. All reagents and solvents were obtained from commercial sources and used without further purification. 2-methyl-3H-indolium salt **1**^[1] and (Z)-N¹-(2-bromo-1-phenylethylidene) benzohydrazide **2**^[2] were prepared according to the literature procedures.

Reference

- [1]. Y. Zhang, M. Yang, C. Jia, Iodine-Promoted Domino Oxidative Cyclization for the One-Pot Synthesis of Novel Fused Four-Ring Quinoxaline Fluorophores by sp³ CH Functionalization. *Chem. Eur. J.*, 2019, **25**, 13709.
- [2]. S. Gao, J. R. Chen, X. Q. Hu, Copper-Catalyzed Enantioselective Inverse Electron-Demand Hetero-Diels-Alder Reactions of Diazadienes with Enol Ethers: Efficient Synthesis of Chiral Pyridazines. *Adv. Synth. Catal.*, 2013, **355**, 3539.

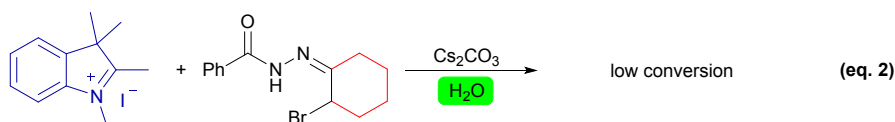
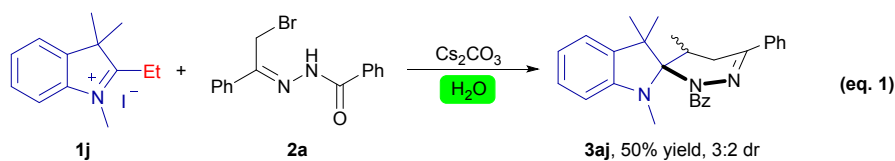
2. General procedure for synthesis of product 3



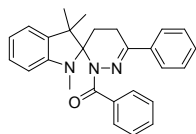
A mixture of 2-methyl-3*H*-indolium salt **1** (0.3 mmol), (*Z*)-*N'*-(2-bromo-1-phenylethylidene)benzohydrazide **2** (0.3 mmol), Cs₂CO₃ (0.36 mmol) and water (3mL) was stirred at room temperature until the reaction completed (monitored by TLC). After the reaction finished, the pink solid **3** was obtained by simple filtration, dried, and further subjected to ¹H NMR, ¹³C NMR, and HRMS analysis.

3. Investigation of other substrates

The 2-ethyl-1,3,3-trimethyl-3*H*-indol-1-ium iodide (**1j**), which bears the 2-ethyl group on the indoline ring was also tested. The reaction of **1j** with **2a** under the optimized conditions completed in 72 h, giving the desired product **3aj** in 50% yield with moderate diastereoselectivity (3:2 d.r.) after filtration and recrystallization (eq. 1). Besides, we also investigated the reaction of **1a** with (*Z*)-*N'*-(2-bromocyclo-hexylidene)benzohydrazide. Only a low conversion was observed in this reaction, which indicates that the alkyl substitution at the terminal site would significantly reduce the reaction activity (eq. 2).



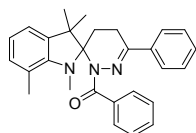
4. Analytical data of compounds 3



3a

phenyl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-

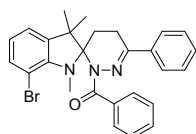
2'-yl)methanone(3a): Yield (115.6mg, 94%); pink solid; m.p. 161.8-163.6 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.59 (d, *J* = 6.3 Hz, 2H), 7.47 (dd, *J* = 7.0, 1.4 Hz, 2H), 7.39 (tt, *J* = 7.0, 1.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.27 (m, 3H), 7.14 (td, *J* = 7.7, 1.4 Hz, 1H), 7.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.77 (td, *J* = 7.0, 0.7 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.08 (ddd, *J* = 18.2, 4.9, 2.1 Hz, 1H), 2.85-2.79 (m, 4H), 2.43 (ddd, *J* = 14.0, 5.6, 2.1 Hz, 1H), 2.39 (td, *J* = 14.0, 5.6, 1H), 1.40 (s, 3H), 1.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.9, 149.7, 142.0, 136.4, 136.4, 135.7, 128.8, 128.4, 127.9, 127.4, 126.3, 126.2, 124.1, 118.5, 116.6, 103.6, 86.4, 47.2, 27.6, 26.4, 24.2, 22.9, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₇N₃O [M+Na]⁺: 432.2046, found: 432.2050.



3b

phenyl(1,3,3,7-tetramethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3b)

*z*in]-2'-yl)methanone(3b): Yield (113.1mg, 89%); pink solid; m.p. 160.0-162.2 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.59 (d, *J* = 9.0 Hz, 2H), 7.47 (dt, *J* = 7.8, 1.8 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.31 – 7.26 (m, 3H), 6.85 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 3.10 (s, 3H), 3.07 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.79 (ddd, *J* = 17.4, 13.8, 5.4 Hz, 1H), 2.45 (s, 3H), 2.42 (ddd, *J* = 14.4, 6.9, 2.4 Hz, 1H), 2.33 (td, *J* = 14.4, 5.4 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.0, 147.6, 142.1, 137.1, 136.6, 135.8, 130.1, 128.7, 128.3, 127.9, 127.4, 126.2, 124.1, 117.0, 116.5, 114.6, 87.1, 46.3, 31.1, 26.9, 24.2, 23.1, 21.9, 19.0. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺: 446.2203, found: 446.2206

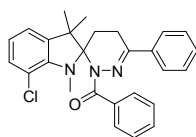


3c

(7-bromo-1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)(phenyl)methanone(3c)

n]-2'-yl)(phenyl)methanone(3c): Yield (139.5mg, 95%); pink solid; m.p. 182.7-183.7 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.60 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 6.0 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 6.6 Hz, 1H), 6.62 (t, *J* = 7.8 Hz, 1H), 3.22 (s, 3H), 3.08 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H), 2.75 (ddd, *J* = 18.0, 14.4, 5.4 Hz, 1H), 2.43 (ddd, *J* = 14.4, 5.4, 2.4 Hz, 1H), 2.34 (td, *J* = 14.4, 5.4 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.0, 146.3, 142.4, 140.4, 136.2, 135.6, 131.7, 128.9, 128.3, 128.0, 127.4, 126.3, 124.1, 118.3, 117.5, 97.9, 86.9, 46.4, 31.1, 26.9, 24.1, 22.9, 21.7. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆Br⁷⁹N₃O [M+H]⁺: 488.1332, found: 488.1331; calculated for C₂₇H₂₆Br⁸¹N₃O

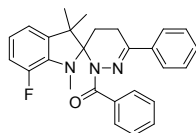
[M+H]⁺: 490.1312, found:490.1316.



3d

(7-chloro-1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)(phenyl)methanone(3d)

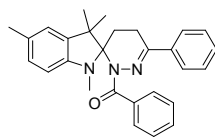
***nj*-2'-yl)(phenyl)methanone(3d)**: Yield (104.9mg, 79%); pink solid; m.p. 168.1-171.9 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.60 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.03 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.68 (t, *J* = 7.8 Hz, 1H), 3.21 (s, 3H), 3.08 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.76 (ddd, *J* = 17.4, 13.8, 5.4 Hz, 1H), 2.43 (ddd, *J* = 14.4, 5.4, 2.4 Hz, 1H), 2.34 (td, *J* = 13.8, 5.4 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.0, 144.9, 142.3, 140.0, 136.2, 135.6, 128.9, 128.5, 128.4, 128.0, 127.4, 126.3, 124.1, 117.9, 117.0, 110.8, 86.9, 46.6, 30.7, 26.9, 24.0, 23.0, 21.7. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆ClN₃O [M+Na]⁺: 466.1657, found: 466.1652.



3e

(7-fluoro-1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)(phenyl)methanone(3e)

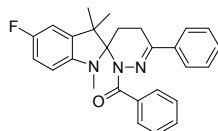
***nj*-2'-yl)(phenyl)methanone(3e)**: Yield (81.2mg, 63%); pink solid; m.p. 174.4-176.7 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.60 (d, *J* = 6.6 Hz, 2H), 7.48 – 7.46 (m, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.27 (m, 3H), 6.85 (dd, *J* = 12.6, 8.4 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.67 (td, *J* = 7.8, 3.6 Hz, 1H), 3.10 – 3.06 (m, 4H), 3.05 (ddd, *J* = 18.0, 13.8, 6.0 Hz, 1H), 2.42 (ddd, *J* = 13.8, 5.4, 1.8 Hz, 1H), 2.36 (td, *J* = 13.8, 4.8 Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.1, 146.7, 145.1, 142.3, 140.2(d, *J*_{C,F} = 24.0 Hz), 136.4, 136.0(d, *J*_{C,F} = 30.0 Hz), 135.6, 128.8, 128.3, 128.0, 127.4, 126.2, 124.1, 116.9(d, *J*_{C,F} = 24.0 Hz), 114.3(d, *J*_{C,F} = 6.0 Hz), 114.0(d, *J*_{C,F} = 84.0 Hz), 86.8, 47.8, 29.6, 29.6, 26.5, 23.7, 22.9, 21.7. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆FN₃O [M+Na]⁺: 450.1952, found: 450.1956.



3f

phenyl(1,3,3,5-tetramethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3f)

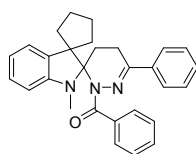
***nj*-2'-yl)methanone(3f)**: Yield (113.6mg, 89%); pink solid; m.p. 146.8-148.3 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.60 – 7.59 (m, 2H), 7.48 – 7.45 (m, 2H), 7.41 – 7.38 (m, 1H), 7.35 – 7.33 (m, 2H), 7.31 – 7.27 (m, 3H), 6.93 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 7.7 Hz, 1H), 3.07 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.85 – 2.78 (m, 4H), 2.41 (ddd, *J* = 14.0, 5.6, 2.1 Hz, 1H), 2.37 (td, *J* = 14.0, 4.9 Hz, 1H), 2.31 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.9, 147.6, 142.0, 136.5, 136.4, 135.8, 128.7, 128.4, 127.9, 127.4, 126.6, 126.6, 126.2, 125.4, 124.1, 119.7, 103.3, 86.8, 47.3, 27.8, 26.5, 24.3, 22.9, 21.8, 20.1. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺: 446.2203, found: 446.2207.



3g

(5-fluoro-1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)(phenyl)methanone(3g):

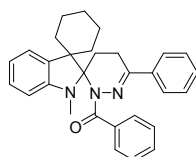
Yield (109.8mg, 86%); pink solid; m.p. 163.5-165.0 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.58 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.46 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.42 – 7.39 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.27 (m, 3H), 6.80 (ddd, *J* = 9.6, 8.4, 2.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 3.0 Hz, 1H), 6.25 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.08 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.82 – 2.76 (m, 4H), 2.42 (ddd, *J* = 13.8, 5.4, 1.8 Hz, 1H), 2.36 (td, *J* = 13.8, 5.4 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.1, 156.2, 154.7, 145.9, 142.2, 137.8(d, *J*_{C,F} = 30.0 Hz), 136.3, 135.6, 128.9, 128.4, 128.0, 127.4, 126.2, 124.1, 111.7(d, *J*_{C,F} = 90.0 Hz), 106.8(d, *J*_{C,F} = 96.0 Hz), 103.1(d, *J*_{C,F} = 36.0 Hz), 86.8, 47.3, 27.9, 26.3, 24.4, 22.7, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆FN₃O [M+Na]⁺: 450.1952, found: 450.1957.



3h

(1-methyl-6''-phenyl-4'',5''-dihydro-2''H-dispiro[cyclopentane-1,3'-indoline-2',3''-pyridazin]-2''-yl)(phenyl)methanone(3h):

Yield (125.0mg, 96%); pink solid; m.p. 153.4-154.8 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.56 (d, *J* = 6.6 Hz, 2H), 7.48 (dt, *J* = 7.8, 1.8 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.27 (m, 3H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.73 (t, *J* = 7.8 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 3.07 (ddd, *J* = 18.0, 4.8, 3.0 Hz, 1H), 2.84 (s, 3H), 2.72 (ddd, *J* = 18.0, 13.2, 7.2 Hz, 1H), 2.45 – 2.37 (m, 2H), 2.17 – 2.09 (m, 3H), 2.03 – 1.98 (m, 1H), 1.92 – 1.86 (m, 1H), 1.81 – 1.73 (m, 1H), 1.70 – 1.63 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 170.7, 149.4, 142.1, 138.0, 136.5, 135.7, 128.6, 128.3, 127.9, 127.4, 126.1, 124.2, 119.5, 116.4, 103.2, 85.4, 59.3, 35.7, 34.0, 27.9, 25.4, 23.4, 22.7, 21.2. HRMS (ESI-TOF): *m/z* calculated for C₂₉H₂₉N₃O [M+Na]⁺: 458.2203, found: 458.2208.

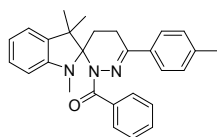


3i

(1-methyl-6''-phenyl-4'',5''-dihydro-2''H-dispiro[cyclohexane-1,3'-indoline-2',3''-pyridazin]-2''-yl)(phenyl)methanone(3i):

Yield (127.0mg, 94%); pink solid; m.p. 153.1-154.5 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.58 – 7.55 (m, 2H), 7.49 – 7.47 (m, 3H), 7.40 – 7.37 (m, 1H), 7.34 – 7.32 (m, 2H), 7.30 – 7.27 (m, 3H), 7.16 (td, *J* = 7.8, 1.2 Hz, 1H), 6.74 (td, *J* = 7.2, 1.2 Hz, 1H), 6.42 (dd, *J* = 7.8, 0.6 Hz, 1H), 3.08 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H), 2.92 (ddd, *J* = 18.0, 14.4, 5.4 Hz, 1H), 2.81 (s, 3H), 2.48 (ddd, *J* = 14.4, 5.4, 2.4 Hz, 1H), 2.36 (td, *J* = 14.4, 5.4 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.97 – 1.91 (m, 1H), 1.90 – 1.87 (m, 1H), 1.82 (td, *J* = 12.0, 3.0 Hz, 1H), 1.66 (dt, *J* = 13.8, 3.6 Hz, 2H), 1.60 (d, *J* = 12.6 Hz, 1H), 1.27 – 1.25 (m, 1H), 1.24 – 1.18 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.1, 150.6, 141.5, 136.6, 135.8, 134.8, 128.6, 128.3, 127.9, 127.4, 126.1, 124.1, 122.9, 115.7, 103.7, 87.4, 50.0, 32.6, 30.9, 27.9, 24.5, 23.8, 21.9, 21.7, 20.0. HRMS (ESI-TOF): *m/z* calculated for

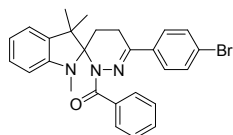
C₃₀H₃₁N₃O [M+Na]⁺ : 472.2359, found: 472.2360.



3j

phenyl(1,3,3-trimethyl-6'-(p-tolyl)-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3j)

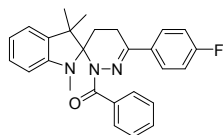
phenyl(1,3,3-trimethyl-6'-(p-tolyl)-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3j) : Yield (116.9mg, 92%); pink solid; m.p. 147.5-149.4 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.58 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.14 (td, *J* = 7.7, 14 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.76 (td, *J* = 7.7, 1.4 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.06 (ddd, *J* = 18.2, 4.9, 2.1 Hz, 1H), 2.82 (s, 3H), 2.79 (ddd, *J* = 18.2, 13.3, 6.3 Hz, 1H), 2.43 – 2.35 (m, 2H), 2.32 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.9, 149.8, 142.1, 138.0, 136.5, 136.4, 133.0, 128.6, 128.4, 128.1, 126.3, 126.1, 124.1, 118.5, 116.5, 103.6, 86.4, 47.2, 27.7, 26.4, 24.2, 22.9, 21.8, 20.2. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺ : 446.2203, found: 446.2206



3k

(6'-(4-bromophenyl)-1,3,3-trimethyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3k)

(6'-(4-bromophenyl)-1,3,3-trimethyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3k) : Yield (134.5mg, 92%); pink solid; m.p. 144.6-147.0 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.55 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.41 – 7.38 (m, 3H), 7.33 (t, *J* = 8.4 Hz, 2H), 7.31 (td, *J* = 9.1, 2.1 Hz, 2H), 7.14 (td, *J* = 7.7, 1.4 Hz, 1H), 7.00 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.77 (td, *J* = 7.7, 1.4 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.03 (ddd, *J* = 18.2, 5.6, 2.1 Hz, 1H), 2.82 (s, 3H), 2.78 (ddd, *J* = 18.2, 14.0, 5.6 Hz, 1H), 2.42 (ddd, *J* = 14.0, 5.6, 2.1 Hz, 1H), 2.38 (td, *J* = 14.0, 5.6 Hz, 1H), 1.38 (s, 3H), 1.31 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.8, 149.6, 140.9, 136.3, 136.3, 134.7, 130.5, 130.5, 128.9, 128.3, 126.4, 126.2, 125.7, 122.2, 118.5, 116.7, 103.6, 86.5, 47.3, 27.6, 26.3, 24.1, 22.8, 21.7. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆Br⁷⁹N₃O [M+Na]⁺ : 510.1151, found: 510.1157; calculated for C₂₇H₂₆Br⁸¹N₃O [M+Na]⁺ : 512.1131, found 510.1135.

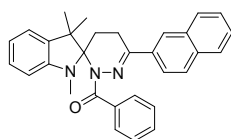


3l

(6'-(4-fluorophenyl)-1,3,3-trimethyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3l)

(6'-(4-fluorophenyl)-1,3,3-trimethyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3l) : Yield (121.6mg, 95%); pink solid; m.p. 147.5-152.0 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.56 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.41 – 7.38 (m, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.14 (td, *J* = 7.8, 1.2 Hz, 1H), 7.00 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.96 (t, *J* = 8.4 Hz, 2H), 6.77 (td, *J* = 7.2, 1.2 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 3.04 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.82 (s, 3H), 2.80 – 2.76 (m, 1H), 2.44 – 2.35 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.9, 164.0, 162.4, 150.7, 142.1, 137.4(d, *J*_{C,F} = 60.0 Hz), 133.90, 129.8, 129.3, 127.4, 127.2, 127.0(d, *J*_{C,F} = 36.0 Hz), 119.5, 117.7, 115.4(d, *J*_{C,F} = 90.0 Hz), 104.7, 87.4, 48.3, 28.7, 27.4, 25.2, 23.9,

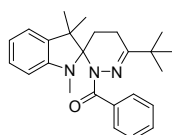
22.9. HRMS (ESI-TOF): m/z calculated for $C_{27}H_{26}N_3O$ $[M+Na]^+$: 450.1952, found: 450.1957.



3m

phenyl(1,3,3-trimethyl-6'-(naphthalen-2-yl)-4',5'-dihydro-2'H-spiro[indoline-2,

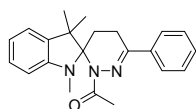
3'-pyridazin]-2'-yl)methanone(3m): Yield (119.4mg, 87%); pink solid; m.p. 153.0-154.1 °C; 1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.95 (s, 1H), 7.81 – 7.77 (m, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 9.0 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.16 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 6.6 Hz, 1H), 6.79 (t, J = 7.8 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 3.25 (ddd, J = 18.0, 5.4, 3.0 Hz, 1H), 2.94 (ddd, J = 18.0, 13.2, 6.0 Hz, 1H), 2.87 (s, 3H), 2.50 – 2.42 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 170.9, 149.7, 142.0, 136.5, 136.4, 133.3, 132.5, 132.0, 128.8, 128.4, 127.3, 127.1, 126.6, 126.4, 126.2, 125.6, 125.3, 123.8, 121.7, 118.5, 116.6, 103.6, 86.6, 47.3, 27.7, 26.4, 24.2, 22.9, 21.7. HRMS (ESI-TOF): m/z calculated for $C_{31}H_{29}N_3O$ $[M+Na]^+$: 482.2203, found: 482.2205.



3n

(6'-(tert-butyl)-1,3,3-trimethyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)

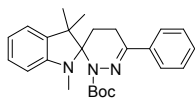
(phenyl)methanone(3n): Yield (72.1mg, 62%); pink solid; m.p. 151.9-154.0 °C; 1H NMR (700 MHz, $CDCl_3$) δ (ppm) 7.45 – 7.44 (m, 2H), 7.30 – 7.27 (m, 1H), 7.25 – 7.24 (m, 2H), 7.11 (td, J = 7.7, 1.4 Hz, 1H), 6.97 (dd, J = 7.0, 1.4 Hz, 1H), 6.74 (td, J = 7.7, 1.4 Hz, 1H), 6.36 (dd, J = 7.7, 0.7 Hz, 1H), 2.78 (s, 3H), 2.62 (ddd, J = 18.2, 4.9, 2.1 Hz, 1H), 2.34 (ddd, J = 17.5, 14.0, 4.9 Hz, 1H), 2.26 (ddd, J = 14.0, 5.6, 1.4 Hz, 1H), 2.14 (td, J = 14.0, 4.9 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 0.97 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 171.06, 153.30, 149.87, 137.08, 136.48, 127.97, 127.88, 126.24, 125.81, 118.31, 118.30, 116.35, 103.47, 85.79, 47.10, 37.03, 27.62, 26.70, 26.48, 24.56, 22.87, 19.91. HRMS (ESI-TOF): m/z calculated for $C_{25}H_{31}N_3O$ $[M+H]^+$: 390.2540, found: 390.2539.



3o

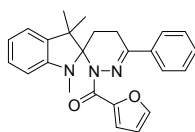
1-(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-

yl)ethan-1-one(3o) : Yield (89.5mg, 86%); pink solid; m.p. 161.5-162.4 °C; 1H NMR (700 MHz, $CDCl_3$) δ (ppm) 7.78 (d, J = 7.0 Hz, 2H), 7.44 – 7.41 (m, 2H), 7.40 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.71 (t, J = 7.7 Hz, 1H), 6.40 (d, J = 7.7 Hz, 1H), 3.05 (ddd, J = 17.5, 4.9, 2.1 Hz, 1H), 2.76-2.71 (m, 4H), 2.38 (s, 3H), 2.33 (ddd, J = 14.0, 4.9, 2.1 Hz, 1H), 2.24 (td, J = 14.0, 5.6 Hz, 1H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 172.9, 150.0, 143.1, 136.3, 136.0, 128.1, 127.5, 126.4, 124.2, 118.2, 116.3, 103.8, 86.7, 47.0, 27.9, 26.5, 24.3, 23.7, 22.6, 21.7. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{25}N_3O$ $[M+Na]^+$: 370.4512, found: 370.4517.



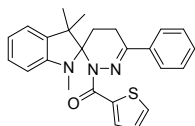
3p *tert-butyl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazine]-2'-carboxylate(3p)*

azine]-2'-carboxylate(3p) : Yield (103.4mg, 85%); pink solid; m.p. 137.9-139.0 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.83 (d, *J* = 7.2 Hz, 2H), 7.40 – 7.37(m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 3.00 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.78 (s, 3H), 2.71 (ddd, *J* = 18.0, 13.8, 5.4 Hz, 1H), 2.28 (ddd, *J* = 14.4, 6.0, 2.4 Hz, 1H), 2.21 (td, *J* = 13.8, 5.4 Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H), 1.23 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 153.9, 150.0, 143.8, 137.9, 137.5, 128.8, 128.5, 127.4, 125.4, 120.2, 117.1, 104.8, 86.8, 81.5, 48.5, 28.6, 28.3, 27.9, 26.3, 24.1, 23.1. HRMS (ESI-TOF): *m/z* calculated for C₂₅H₃₁N₃O₂ [M+Na]⁺ : 428.2308, found: 428.2312.



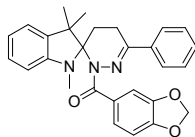
3q *furan-2-yl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazine]-2'-yl)methanone(3q)*

in]-2'-yl)methanone(3q) : Yield (114.2mg, 95%); pink solid; m.p. 137.1-139.7 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.73 (d, *J* = 6.3 Hz, 2H), 7.52 (s, 1H), 7.44 – 7.42 (m, 2H), 7.41 – 7.39 (m, 1H), 7.13 (d, *J* = 4.2 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.73 (t, *J* = 7.0 Hz, 1H), 6.47 (dd, *J* = 3.5, 1.4 Hz, 1H), 6.41 (d, *J* = 7.7 Hz, 1H), 3.13 (ddd, *J* = 18.2, 4.9, 2.1 Hz, 1H), 2.82 (ddd, *J* = 18.2, 13.3, 6.3 Hz, 1H), 2.77 (s, 3H), 2.43 – 2.36 (m, 2H), 1.37 (s, 3H), 1.29 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 159.5, 149.7, 147.0, 144.2, 143.7, 136.1, 136.0, 128.2, 127.6, 126.4, 124.7, 118.5, 118.0, 116.5, 110.3, 103.9, 87.2, 47.4, 27.8, 26.5, 24.3, 22.8, 22.1. HRMS (ESI-TOF): *m/z* calculated for C₂₅H₂₅N₃O₂ [M+Na]⁺ : 422.1839, found: 422.1843.



3r *thiophen-2-yl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazine]-2'-yl)methanone(3r)*

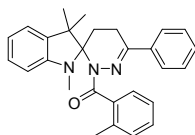
dazin]-2'-yl)methanone(3r) : Yield (108.2mg, 87%); pink solid; m.p. 156.4-157.2 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.97 (dd, *J* = 3.5, 1.4 Hz, 1H), 7.86 – 7.84 (m, 2H), 7.52 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.44 – 7.42 (m, 1H), 7.17 (td, *J* = 7.7, 0.7 Hz, 1H), 7.01 (dd, *J* = 5.6, 4.2 Hz, 1H), 6.98 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.77 (td, *J* = 7.0, 0.7 Hz, 1H), 6.43 (dd, *J* = 7.7, 0.7 Hz, 1H), 3.17 (ddd, *J* = 18.2, 4.9, 2.1 Hz, 1H), 2.82 (ddd, *J* = 18.2, 13.3, 6.3 Hz, 1H), 2.77 (s, 3H), 2.43 – 2.36 (m, 2H), 1.38 (s, 3H), 1.31 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 162.2, 149.7, 145.0, 136.4, 135.6, 134.8, 134.8, 133.9, 132.7, 128.3, 127.4, 126.4, 125.8, 124.9, 118.5, 118.5, 116.5, 103.6, 87.2, 47.4, 27.9, 26.7, 24.6, 22.9, 22.7. HRMS (ESI-TOF): *m/z* calculated for C₂₅H₂₅N₃OS [M+Na]⁺ : 438.1611, found: 438.1616.



3s

benzo[d][1,3]dioxol-5-yl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoli

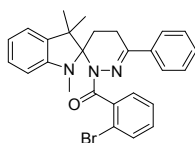
ne-2,3'-pyridazin]-2'-yl)methanone(3s) : Yield (104.7mg, 77%); pink solid; m.p. 136.3-138.4 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.54 (dd, *J* = 7.2, 3.6 Hz, 2H), 7.33-7.31 (m, 3H), 7.21 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.14 (t, *J* = 1.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.77 (t, *J* = 8.4 Hz, 2H), 6.37 (d, *J* = 7.8 Hz, 1H), 5.99 (dd, *J* = 6.6, 1.2 Hz, 2H), 3.08 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.83 (ddd, *J* = 18.0, 13.8, 6.0 Hz, 1H), 2.78 (s, 3H), 2.42 – 2.34 (m, 2H), 1.38 (s, 3H), 1.30 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 170.7, 150.7, 149.1, 146.7, 142.8, 137.5, 136.8, 130.8, 129.0, 128.5, 127.3, 125.2, 125.1, 119.5, 117.6, 110.6, 107.1, 104.5, 101.3, 87.4, 48.3, 28.6, 27.4, 25.2, 23.9, 23.0. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₇N₃O₃ [M+Na]⁺ : 476.1945, found: 476.1947.



3t

o-tolyl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-

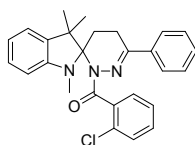
2'-yl)methanone(3t) : Yield (116.9mg, 92%); pink solid; m.p. 190.3-191.3 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.29 (d, *J* = 7.0 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.22 – 7.21 (m, 1H), 7.16 (t, *J* = 7.7 Hz, 2H), 7.13 – 7.11 (m, 2H), 7.00 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.77 (t, *J* = 7.7 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 3.05 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.92 (s, 3H), 2.75 (ddd, *J* = 18.2, 14.0, 5.6 Hz, 1H), 2.40 (ddd, *J* = 14.0, 5.6, 2.1 Hz, 1H), 2.33 (td, *J* = 14.0, 4.9 Hz, 1H), 2.27 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 172.5, 149.8, 142.8, 138.9, 136.2, 135.6, 132.7, 128.3, 127.9, 127.3, 126.8, 126.5, 125.6, 124.0, 123.9, 118.5, 116.6, 103.9, 86.8, 47.3, 28.2, 26.5, 24.2, 22.8, 21.6, 19.1. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺ : 446.2203, found: 446.2207



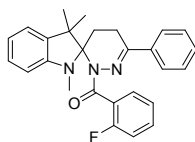
3u

(2-bromophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-

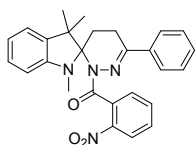
pyridazin]-2'-yl)methanone(3u): Yield (131.1mg, 89%); pink solid; m.p. 185.2-186.2 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.54 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 2H), 7.27 – 7.22 (m, 4H), 7.19 – 7.15 (m, 3H), 6.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.76 (t, *J* = 7.7 Hz, 1H), 6.47 (d, *J* = 7.7 Hz, 1H), 3.07 (dt, *J* = 18.2, 3.5 Hz, 1H), 2.99 (s, 3H), 2.80 – 2.75 (m, 1H), 2.43 – 2.36 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 169.8, 149.8, 143.6, 140.8, 135.9, 135.6, 130.8, 128.0, 127.3, 126.6, 125.8, 124.1, 118.5, 118.0, 116.5, 104.1, 87.1, 47.4, 28.7, 26.4, 23.8, 22.7, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆Br⁷⁹N₃O [M+H]⁺ : 488.1332, found: 488.1333; calculated for C₂₇H₂₆Br⁸¹N₃O [M+H]⁺ : 490.1312, found: 490.1311.



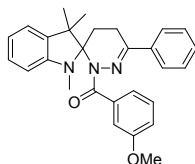
3v **(2-chlorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone (3v)**: Yield (116.1mg, 87%); pink solid; m.p. 177.8-178.3 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.36 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.31 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.25 – 7.23 (m, 2H), 7.22 – 7.21 (m, 2H), 7.15 (td, *J* = 7.7, 1.4 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.76 (td, *J* = 7.7, 1.4 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 3.06 (dt, *J* = 18.2, 3.5 Hz, 1H), 2.95 (s, 3H), 2.76 (dt, *J* = 18.2, 9.1 Hz, 1H), 2.38 (dd, *J* = 9.8, 3.5 Hz, 2H), 1.38 (s, 3H), 1.35 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 169.2, 149.8, 143.6, 138.6, 136.0, 135.6, 129.0, 128.0, 127.6, 127.3, 126.5, 125.3, 124.1, 118.5, 116.6, 104.0, 87.2, 47.3, 28.3, 26.4, 23.9, 22.7, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆ClN₃O [M+Na]⁺: 466.1657, found: 466.1654.



3w **(2-fluorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro [indoline-2,3'-pyridazin]-2'-yl)methanone(3w)**: Yield (121.0mg, 94%); pink solid; m.p. 176.3-178.6 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.39 – 7.38 (m, 1H), 7.37 – 7.36 (m, 2H), 7.35 – 7.33 (m, 1H), 7.30 – 7.27 (m, 1H), 7.26 – 7.22 (m, 2H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (td, *J* = 7.6, 0.8 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.99 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.76 (td, *J* = 7.6, 1.2 Hz, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 3.05 (ddd, *J* = 17.6, 4.8, 2.4 Hz, 1H), 2.86 (s, 3H), 2.77 (ddd, *J* = 18.0, 13.2, 6.0 Hz, 1H), 2.43 – 2.31 (m, 2H), 1.38 (s, 3H), 1.33 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 167.7, 158.5, 156.0, 149.8, 143.5, 135.9(d, *J*_{C,F} = 188.0 Hz), 129.7(d, *J*_{C,F} = 32.0 Hz), 128.5(d, *J*_{C,F} = 16.0 Hz), 128.0, 127.3, 126.4, 124.1, 122.8(d, *J*_{C,F} = 12.0 Hz), 118.5, 116.6, 113.6(d, *J*_{C,F} = 92.0 Hz), 103.7, 87.2, 47.2, 28.7, 27.7, 26.5, 24.0, 22.8, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆FN₃O [M+Na]⁺: 450.1952, found: 450.1956.

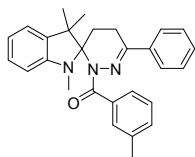


3x **(2-nitrophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-2'-yl)methanone(3x)**: Yield (113.5mg, 83%); pink solid; m.p. 172.1-174.1 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.65 (td, *J* = 7.6, 1.6 Hz, 1H), 7.53 (td, *J* = 8.4, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 3H), 7.23 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.05 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.82 (td, *J* = 7.2, 0.8 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 3.13 – 3.07 (m, 4H), 2.79 (ddd, *J* = 18.0, 11.6, 0.8 Hz, 1H), 2.51 – 2.40 (m, 2H), 1.42 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 168.4, 149.8, 144.6, 144.4, 135.7, 135.4, 135.1, 132.7, 128.3, 127.7, 127.5, 127.3, 126.7, 124.0, 122.3, 118.5, 116.5, 104.3, 87.7, 47.7, 28.7, 28.3, 26.4, 23.7, 22.4, 21.9. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆N₄O₃ [M+Na]⁺: 477.1897, found: 477.1904.



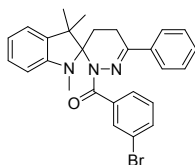
3y **(3-methoxyphenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-**

2,3'-pyridazin]-2'-yl)methanone(3y): Yield (108.9mg, 83%); pink solid; m.p. 167.7-169.0 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.50 – 7.48 (m, 2H), 7.31 – 7.27 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.15 – 7.13 (m, 2H), 7.00 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.95 (ddd, *J* = 8.4, 2.8, 1.4 Hz, 1H), 6.78 (td, *J* = 7.7, 0.7 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 3.08 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.86 – 2.80 (m, 4H), 2.42 (ddd, *J* = 14.0, 6.3, 2.8 Hz, 1H), 2.39 (td, *J* = 14.0, 4.9 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.6, 157.9, 149.7, 142.0, 136.4, 135.8, 127.9, 127.4, 126.9, 126.4, 124.2, 121.1, 118.5, 116.6, 115.4, 113.2, 103.6, 86.5, 54.4, 47.2, 27.6, 26.4, 24.2, 22.9, 21.9. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O₂ [M+Na]⁺ : 462.2152, found: 462.2157.



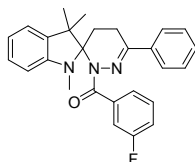
3z ***m*-tolyl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-**

2'-yl)methanone(3z): Yield (112.8mg, 89%); pink solid; m.p. 164.3-166.4 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.50 – 7.49 (m, 2H), 7.44 – 7.43 (m, 1H), 7.40 – 7.39 (m, 1H), 7.31 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 7.14 (td, *J* = 7.7, 1.4 Hz, 1H), 7.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.77 (td, *J* = 7.0, 0.7 Hz, 1H), 6.40 (dd, *J* = 8.4, 1.4 Hz, 1H), 3.08 (ddd, *J* = 18.2, 4.9, 2.1 Hz, 1H), 2.85 – 2.80 (m, 4H), 2.42 (ddd, *J* = 14.0, 6.3, 2.1 Hz, 1H), 2.39 (td, *J* = 14.0, 5.6 Hz, 1H), 2.34 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.0, 149.8, 141.9, 136.4, 136.2, 135.9, 135.9, 129.5, 129.2, 127.9, 127.4, 126.3, 125.9, 125.7, 124.1, 118.5, 116.6, 103.6, 86.4, 47.2, 27.7, 26.4, 24.2, 22.9, 21.8, 20.2. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺ : 446.2203, found: 446.2204.



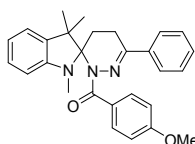
3aa **(3-bromophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-**

pyridazin]-2'-yl)methanone(3aa): Yield (126.1mg, 86%); pink solid; m.p. 158.3-159.2 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.76 (t, *J* = 1.4 Hz, 1H), 7.54 – 7.47 (m, 4H), 7.34 – 7.30 (m, 3H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.16 (td, *J* = 7.7, 1.4 Hz, 1H), 7.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.78 (td, *J* = 7.7, 1.4 Hz, 1H), 6.41 (d, *J* = 7.7 Hz, 1H), 3.10 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.86 – 2.80 (m, 4H), 2.43 (ddd, *J* = 14.0, 5.6, 2.1 Hz, 1H), 2.39 (td, *J* = 14.0, 4.9 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 169.2, 149.6, 143.1, 138.3, 136.2, 135.5, 131.6, 131.5, 128.2, 127.8, 127.8, 127.5, 127.0, 126.4, 124.2, 120.1, 118.5, 116.7, 103.7, 86.8, 47.3, 27.7, 26.4, 24.1, 22.8, 21.8. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆Br⁷⁹N₃O [M+H]⁺ : 488.1332, found: 480.1331; calculated for C₂₇H₂₆Br⁸¹N₃O [M+H]⁺ : 490.1312, found: 490.1318.



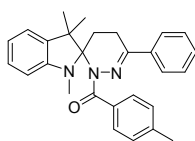
3ab (3-fluorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-

pyridazin]-2'-yl)methanone(3ab): Yield (99.8mg, 78%); pink solid; m.p. 151.7-153.3 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.49 – 7.46 (m, 2H), 7.37 – 7.34 (m, 1H), 7.33 – 7.28 (m, 5H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 3.10 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.85 – 2.79 (m, 4H), 2.45 – 2.35 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 170.6, 162.7, 161.1, 150.7, 143.9, 137.3, 136.5, 129.2, 128.8(d, *J*_{C,F} = 30.0 Hz), 128.5, 127.5, 125.2, 125.0(d, *J*_{C,F} = 12.0 Hz), 119.6, 117.7, 116.5(d, *J*_{C,F} = 48.0 Hz), 116.5(d, *J*_{C,F} = 228.0 Hz), 104.7, 87.7, 48.3, 28.7, 27.4, 25.2, 23.9, 22.9. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆FN₃O [M+Na]⁺: 450.1952, found: 450.1955.



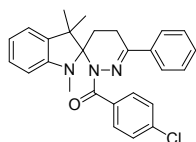
3ac (4-methoxyphenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-

pyridazin]-2'-yl)methanone(3ac): Yield (121.6mg, 92%); pink solid; m.p. 148.1-149.2 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.64 (d, *J* = 9.1 Hz, 2H), 7.55 (d, *J* = 3.5 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.31 (d, *J* = 3.5 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 2H), 7.13 (td, *J* = 7.7, 1.4 Hz, 1H), 6.99 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.85 (dd, *J* = 7.7, 1.4 Hz, 2H), 6.77 (t, *J* = 7.0 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.08 (ddd, *J* = 18.2, 5.6, 2.1 Hz, 1H), 2.83 (ddd, *J* = 17.5, 13.3, 5. Hz, 1H), 2.78 (s, 3H), 2.43 – 2.41 (m, 1H), 2.39 (td, *J* = 14.0, 4.9 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.0, 160.1, 149.7, 141.4, 136.5, 135.9, 131.0, 128.1, 127.8, 127.4, 126.3, 124.1, 118.5, 116.5, 111.4, 103.4, 86.2, 54.3, 47.3, 27.6, 26.3, 24.3, 22.9, 21.9. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O₂ [M+Na]⁺: 462.2152, found: 462.2157.



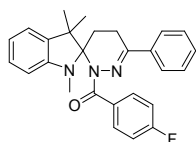
3ad *p*-tolyl(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyridazin]-

2'-yl)methanone(3ad): Yield (119.1mg, 94%); pink solid; m.p. 149.8-152.2 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.50 – 7.50 (m, 4H), 7.31 – 7.29 (m, 3H), 7.15 – 7.12 (m, 3H), 6.99 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.77 (td, *J* = 7.2, 1.2 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 3.08 (ddd, *J* = 18.0, 5.4, 2.4 Hz, 1H), 2.86 – 2.79 (m, 4H), 2.42 (ddd, *J* = 14.4, 6.6, 2.4 Hz, 1H), 2.40 – 2.35 (m, 4H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 171.7, 150.8, 142.7, 140.1, 137.5, 136.9, 134.2, 129.9, 128.8, 128.4, 127.9, 127.3, 125.2, 119.5, 117.6, 104.5, 87.3, 48.3, 28.6, 27.4, 25.3, 23.9, 22.9, 21.5. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+Na]⁺: 446.2203, found: 446.2205.



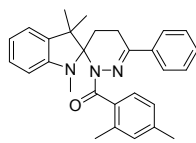
3ae (4-chlorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro [indoline-2,3'-

pyridazin]-2'-yl)methanone(**3ae**): Yield (115.7mg, 87%); pink solid; m.p. 137.8-139.3 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.56 – 7.54 (m, 2H), 7.50 – 7.48 (m, 2H), 7.33 – 7.31 (m, 5H), 7.15 (td, *J* = 7.7, 1.4 Hz, 1H), 7.00 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.78 (td, *J* = 7.7, 0.7 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.10 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.85 – 2.79 (m, 4H), 2.43 (ddd, *J* = 14.7, 6.3, 2.8 Hz, 1H), 2.38 (td, *J* = 14.0, 4.9 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 170.68, 150.65, 143.70, 137.32, 136.54, 135.79, 131.03, 131.01, 129.16, 128.52, 127.45, 127.42, 125.14, 119.52, 117.70, 104.60, 87.64, 48.29, 28.64, 27.40, 25.18, 23.86, 22.88. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆ClN₃O [M+Na]⁺: 466.1657, found: 466.1660.



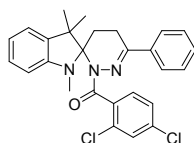
3af (4-fluorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro [indoline-2,3'-

pyridazin]-2'-yl)methanone(**3af**): Yield (115.6mg, 90%); pink solid; m.p. 169.6-172.1 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.64 – 7.61 (m, 2H), 7.50 – 7.49 (m, 2H), 7.33 – 7.29 (m, 3H), 7.14 (td, *J* = 7.0, 1.4 Hz, 1H), 7.02 (t, *J* = 8.4 Hz, 2H), 7.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.78 (td, *J* = 7.7, 0.7 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.10 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 2.85 – 2.78 (m, 4H), 2.43 (ddd, *J* = 14.0, 6.3, 2.1 Hz, 1H), 2.38 (td, *J* = 14.0, 4.9 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 169.6, 163.3, 161.9, 149.6, 142.4, 136.3, 135.6, 132.3(d, *J*_{C,F} = 14.0 Hz), 130.9(d, *J*_{C,F} = 28.0 Hz), 128.1, 127.5, 126.4, 124.1, 118.5, 116.7, 113.2(d, *J*_{C,F} = 84.0 Hz), 103.5, 86.5, 47.3, 27.6, 26.4, 24.2, 22.9, 21.9. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₆FN₃O [M+Na]⁺: 450.1952, found: 450.1954.



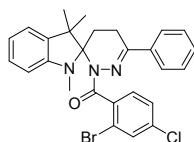
3ag (2,4-dimethylphenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,

3'-pyridazin]-2'-yl)methanone(**3ag**): Yield (125.4mg, 96%); pink solid; m.p. 181.7-183.2 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.33 – 7.31 (m, 2H), 7.26 – 7.22 (m, 3H), 7.14 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.98 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.96 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 3.04 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H), 2.90 (s, 3H), 2.74 (ddd, *J* = 18.6, 14.4, 6.0 Hz, 1H), 2.39 (ddd, *J* = 13.8, 5.4, 1.8 Hz, 1H), 2.35 – 2.29 (m, 4H), 2.22 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 173.6, 150.8, 143.5, 137.6, 137.3, 136.9, 136.7, 133.9, 130.1, 128.9, 128.4, 127.5, 126.9, 125.5, 125.0, 119.5, 117.5, 104.9, 87.7, 48.3, 29.2, 27.5, 25.3, 23.9, 22.7, 21.3, 20.2. HRMS (ESI-TOF): *m/z* calculated for C₂₉H₃₁N₃O [M+Na]⁺: 460.2359, found: 460.2361.



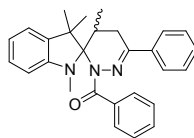
3ah (2,4-dichlorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoli ne-

2,3'-pyridazin]-2'-yl)methanone(3ah): Yield (115.8mg, 81%); pink solid; m.p. 172.9-173.7 °C; ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.39 (d, *J* = 2.1 Hz, 1H), 7.34 – 7.33 (m, 2H), 7.32 – 7.30 (m, 1H), 7.29 – 7.27 (m, 2H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.16 (td, *J* = 7.7, 1.4 Hz, 2H), 6.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.76 (td, *J* = 7.7, 1.4 Hz, 1H), 6.45 (dd, *J* = 7.7, 0.7 Hz, 1H), 3.09 – 3.06 (m, 1H), 2.93 (s, 3H), 2.80 – 2.75 (m, 1H), 2.40 – 2.36 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 168.3, 149.67, 144.3, 137.2, 135.9, 135.4, 133.2, 130.0, 128.3, 127.5, 127.4, 126.6, 125.7, 124.1, 118.5, 116.7, 104.0, 87.3, 47.3, 28.3, 26.4, 23.8, 22.7, 21.9. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₅Cl₂N₃O [M+Na]⁺ : 500.1267, found: 500.1264.



3ai (2-bromo-4-chlorophenyl)(1,3,3-trimethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoli

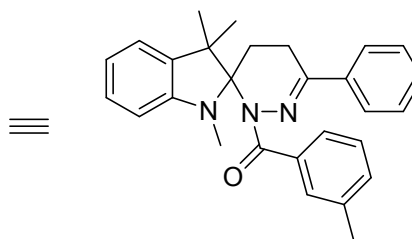
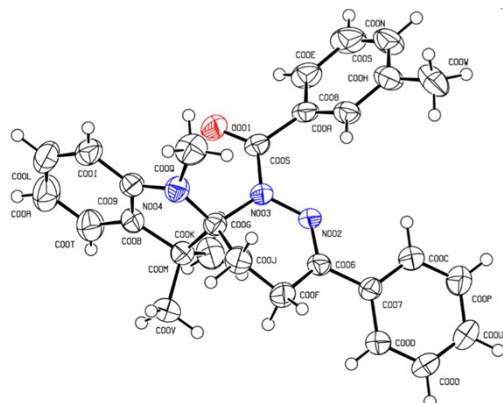
ne-2,3'-pyridazin]-2'-yl)methanone(3ai): Yield (115.5mg, 82%); pink solid; m.p. 176.2-180.7 °C; ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.57 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.32 – 7.30 (m, 1H), 7.29 – 7.27 (m, 2H), 7.25 – 7.24 (m, 1H), 7.16 (td, *J* = 7.8, 1.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.76 (td, *J* = 7.8, 1.2 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 3.08 (dt, *J* = 18.0, 3.6 Hz, 1H), 2.96 (s, 3H), 2.81 – 2.75 (m, 1H), 2.39 (dd, *J* = 7.8, 2.4 Hz, 2H), 1.37 (s, 3H), 1.34 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 169.9, 150.7, 145.3, 140.4, 136.9, 136.4, 134.0, 131.5, 129.3, 128.5, 127.6, 127.2, 125.1, 119.6, 119.5, 117.7, 105.1, 88.4, 48.5, 29.6, 27.4, 24.8, 23.7, 23.0. HRMS (ESI-TOF): *m/z* calculated for C₂₇H₂₅Br⁷⁹ClN₃O [M+Na]⁺ : 544.0762, found: 544.0764; calculated for C₂₇H₂₅Br⁸¹ClN₃O [M+ Na]⁺ : 546.0741, found:546.0742.



3aj phenyl(1,3,3,4'-tetramethyl-6'-phenyl-4',5'-dihydro-2'H-spiro[indoline-2,3'-pyrid

azin]-2'-yl)methanone(3aj): Yield (63.1mg, 50%); pink solid; m.p. 185.0-187.8 °C; The major diastereoisomer of the mixture: ¹H NMR (700 MHz, CDCl₃) δ (ppm) 7.57 (d, *J* = 7.0 Hz, 2H), 7.47 (dd, *J* = 6.3, 2.1 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.30 – 7.27 (m, 5H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.75 (t, *J* = 7.0 Hz, 1H), 6.44 (d, *J* = 7.0 Hz, 1H), 3.09 (dd, *J* = 17.5, 4.9 Hz, 1H), 3.03 – 3.01 (m, 1H), 2.87 (ddd, *J* = 15.4, 7.7, 2.1 Hz, 1H), 2.82 (s, 3H), 1.47 (s, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃) δ (ppm) 171.71, 150.70, 143.56, 137.84, 137.50, 137.17, 136.76, 130.03, 129.68, 129.36, 128.91, 128.39, 127.56, 127.23, 125.16, 119.66, 118.19, 117.34, 104.65, 91.97, 50.07, 35.32, 32.45, 30.68, 27.94, 26.38, 20.10, 16.51. HRMS (ESI-TOF): *m/z* calculated for C₂₈H₂₉N₃O [M+H]⁺ : 424.2383, found: 424.2383.

5. X-ray crystal structure of **3z**



3z, CCDC 2015441

Identification code	exp_6081
Empirical formula	C ₂₈ H ₂₉ N ₃ O
Formula weight	423.54
Temperature/K	294.43(16)
Crystal system	monoclinic
Space group	Cc
a/Å	14.5799(6)
b/Å	20.9306(11)
c/Å	7.7649(4)
α /°	90
β /°	101.063(4)
γ /°	90
Volume/Å ³	2325.56(19)
Z	4
ρ calcg/cm ³	1.210
μ /mm ⁻¹	0.578
F(000)	904.0
Crystal size/mm ³	0.65 × 0.3 × 0.2
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/°	8.448 to 143.59
Index ranges	-17 ≤ h ≤ 17, -25 ≤ k ≤ 17, -9 ≤ l ≤ 8
Reflections collected	4980
Independent reflections	2574 [R_{int} = 0.0324, R_{sigma} = 0.0331]
Data/restraints/parameters	2574/2/293
Goodness-of-fit on F ²	1.046
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0618, wR_2 = 0.1540
Final R indexes [all data]	R_1 = 0.0626, wR_2 = 0.1568
Largest diff. peak/hole / e Å ⁻³	0.20/-0.35
Flack parameter	0.4(4)

6. DFT Calculations

The geometry optimizations for all of the species were performed with the density functional theory (DFT)^[3] at the B3LYP-D3/6-31G(d) level^[4] by using the Gaussian 16 program^[5]. Then, the harmonic vibrational frequencies were analyzed to characterize the nature of the stationary point as a minimum with all positive frequencies or as a transition state with only one imaginary frequency and to provide thermodynamic quantity. Based on the optimized structures, the electronic energy (E_{electron}) and solvation free energy (ΔG_{solv}) were calculated at the B3LYP-D3/6-311G(d,p) level of theory in aqueous and dichloromethane medium, respectively, while using SMD solvation model^[6].

To better understand the mechanism details of this [4 + 2] annulation reaction, we carried out computational studies by using the explicit inclusion of waters model (Figure 1) and the continuum solvation models (Figure 2). Interestingly, the DFT calculations elucidated that the reaction undergoes a stepwise ionic annulation rather than a synergetic pathway. Based on the experimental and computational results of this [4 + 2] annulation, the transition state of the first step, which is the rate-determining step, has been depicted in Figure 4. Water, the strong polar and H-bond donor solvent, will result in the reduction of the energy barrier of the first step, and accordingly lead to the increase of reaction rate. Meanwhile, the strong polar solvent results in a stable product with low energy. Figure 3 shows the DFT-optimized structures (bond lengths, Å) of transition state using DCM or water as the solvent.

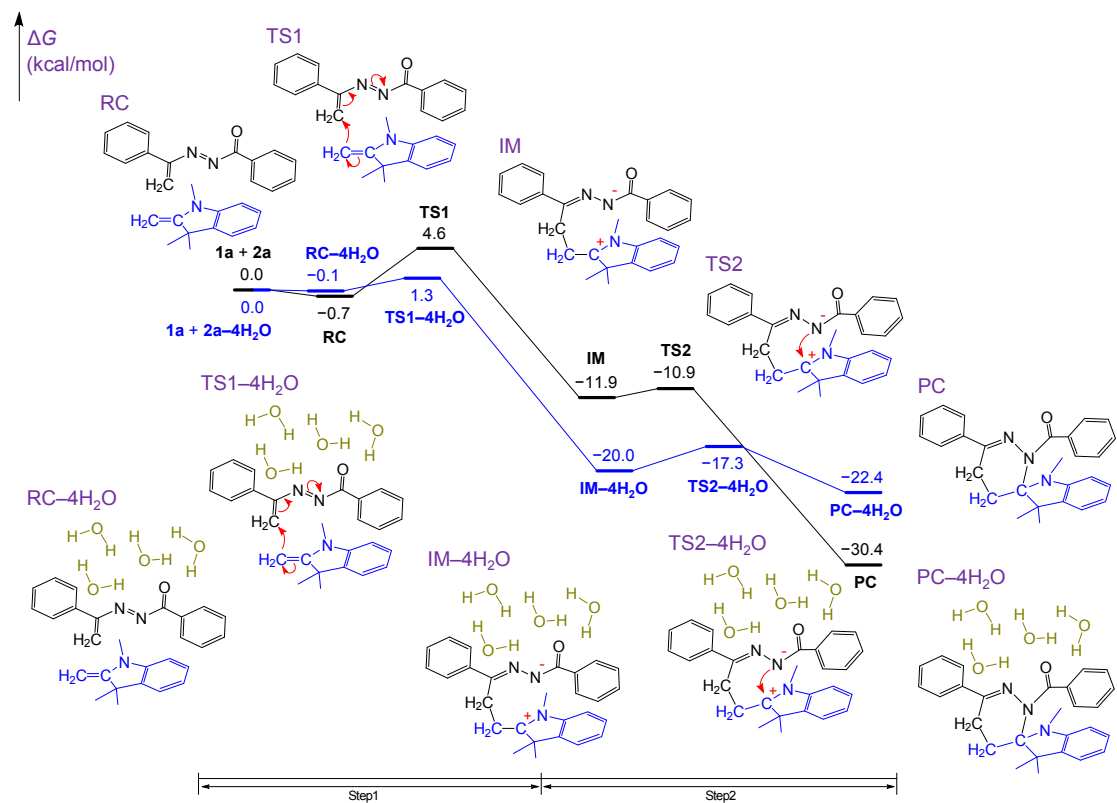


Figure 1. DFT-computed relative energy profiles at the B3LYP-D3/6-31G(d) level of theory.

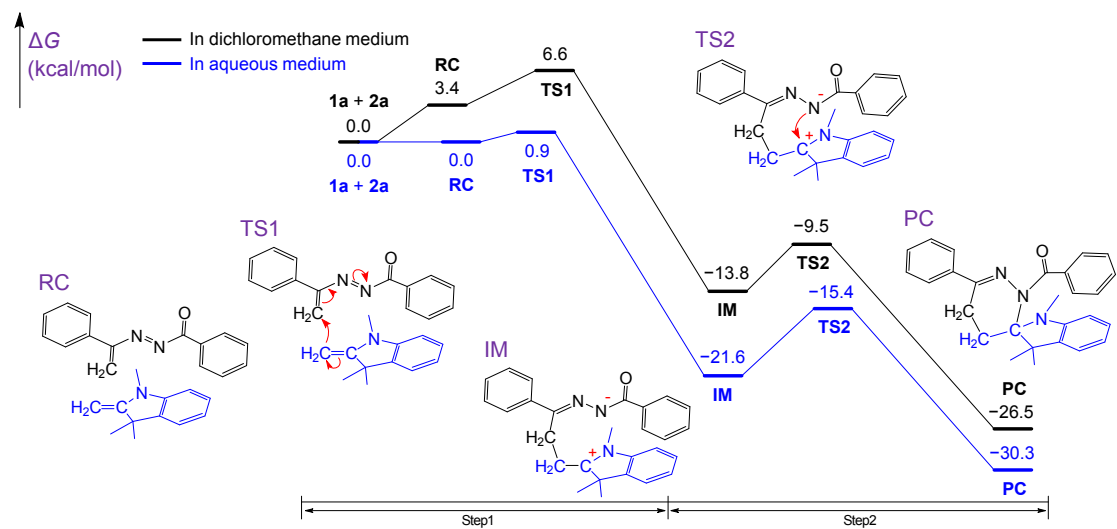


Figure 2. DFT-computed relative energy profiles at the B3LYP-D3/6-311G(d,p)/SMD// B3LYP-D3/6-31G(d) level of theory.

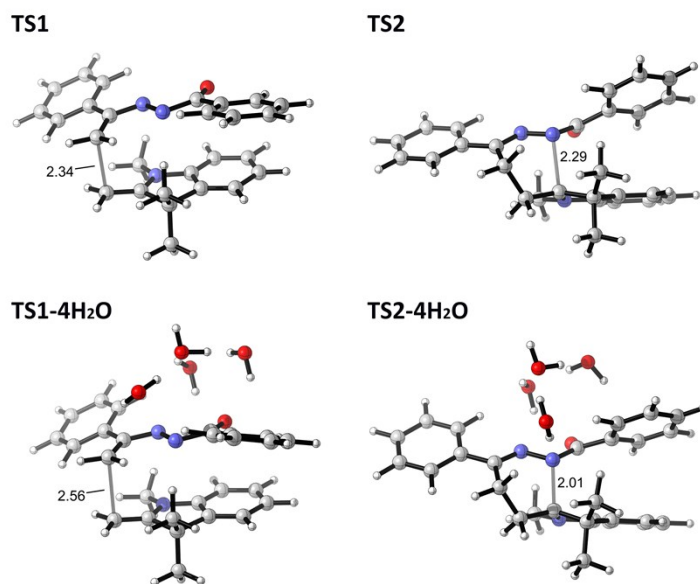


Figure 3. DFT-optimized structures (bond lengths, Å) of transition state.

Reference

- [3]. a) P. Hohenberg, W. Kohn, *Phys. Rev.* 1964, **136**, B864–B871; b) W. Kohn, L. J. Sham, *Phys. Rev.* 1965, **140**, A1133–A1138.
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- [5]. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian 16*, revision B.01, Gaussian, Inc.: Wallingford, CT, 2016.
- [6]. A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* 2009, **113**, 6378–6396.

Cartesian coordinate for theoretical calculation

1. Pathway-1

RC			
C	4.67216800	-1.96414400	-1.08147700
C	3.44418800	-2.00770100	-0.42476500
C	3.18336100	-1.14317300	0.65017800
C	4.17308400	-0.23148900	1.04457400
C	5.39943500	-0.18930400	0.38472200
C	5.65345500	-1.05511900	-0.68129400
H	4.86215300	-2.64058900	-1.91007300
H	2.67156700	-2.69934700	-0.74052800
H	3.96102900	0.47349800	1.84123900
H	6.15232400	0.53019000	0.69419400
H	6.60776900	-1.01751400	-1.19896700
C	1.87760600	-1.18982200	1.34186000
C	1.70145800	-0.94861000	2.65395500
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N	0.82118300	-1.64705700	0.50357200
N	-0.33834000	-1.39393700	0.90028800
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H	-5.90054000	-2.07667400	-0.77127000
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C	-1.08253900	0.28714400	-2.27275000
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C	-0.23388600	2.10228100	1.92397900
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H	0.54309400	4.60258700	1.01514000
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C	2.46218600	2.57298700	0.20432000
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H	2.55591300	3.33753000	0.96651200

TS1

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C	-5.76095800	0.43684500	0.47409300
C	-5.93578400	1.30558500	-0.60334300
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H	-6.91818000	1.43920200	-1.04719400
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C	-1.77547800	-0.02605600	2.22223900
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H	-0.77244300	-0.04418600	2.62340800
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N	0.18931300	1.15202500	0.76048700
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C	2.52813500	1.70847900	0.33614400
C	3.55845700	1.94245800	-0.58491700
C	2.84810400	1.48027800	1.68104800
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C	4.17970700	1.46665800	2.09305700
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H	4.42063600	1.29285500	3.13825100
H	6.23973300	1.66151000	1.48670500
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C	2.97758000	-0.98638400	-2.20510400
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H	2.15088000	-0.12332300	-3.99559400
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H	2.04733200	-4.15673700	0.64618500
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IM

C	5.44831400	1.28694200	1.46752900
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C	1.46472200	-1.49774400	-1.50745800
H	2.25714900	-2.02234900	-0.96342600
H	1.25451600	-2.07764700	-2.41169400
TS2			
C	-5.49865000	1.13917200	-1.59672000
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C	-3.92282400	0.49509200	0.14504100
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C	-6.29806200	-0.00810700	0.36426500
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H	-3.37450200	1.51186600	-1.66282600
H	-4.82874200	-0.52392300	1.82944300
H	-7.10975000	-0.44010900	0.94375700
H	-7.57183000	0.62522600	-1.25710500
C	-2.53306000	0.44719600	0.63342200
C	-2.12147600	-0.26047900	1.88459000
H	-2.96112100	-0.55542900	2.51485200
H	-1.46449600	0.39594000	2.46431300
N	-1.60578200	0.95093000	-0.12558200
N	-0.33881200	0.91049300	0.36222700
C	0.57171100	1.22940600	-0.65217400
O	0.39592700	1.01149100	-1.85227300
C	1.84371200	1.86503900	-0.18596400
C	2.98630300	1.75277000	-0.98738200
C	1.90105100	2.62232900	0.99100300
C	4.18006200	2.35119400	-0.59619700
H	2.91827200	1.17789100	-1.90379200
C	3.09349600	3.23452700	1.37590700
H	1.00118100	2.72625500	1.58810200
C	4.23704000	3.09244000	0.58759200
H	5.06798500	2.24288000	-1.21333300
H	3.12970500	3.82566400	2.28697500
H	5.16809200	3.56469000	0.88978100
C	1.43741000	-1.69787100	-0.93905200
C	2.22300100	-1.50263200	0.20098500
C	3.60397100	-1.45468300	0.09406300
C	4.18466700	-1.59261800	-1.17174400
C	3.38462100	-1.78754800	-2.30256600
C	1.99107300	-1.84244300	-2.20477800
H	4.22338000	-1.29233700	0.97123600
H	5.26358100	-1.53727000	-1.27853100
H	3.84940400	-1.88328000	-3.27928900
H	1.37359400	-1.94951700	-3.08890800
C	1.30771200	-1.49537700	1.40756800
C	1.61510000	-0.48274500	2.50925400
H	0.87706300	-0.56232500	3.31498700
H	2.60014000	-0.69379300	2.93941100
H	1.60524900	0.53404900	2.12887200
C	1.37136500	-2.93149500	2.01666200
H	2.39895400	-3.13062800	2.33412000
H	0.72311600	-3.02445300	2.89370400
H	1.08754100	-3.69103200	1.28203600
C	-0.99807300	-1.71563300	-1.55774100
H	-1.04944000	-0.73048300	-2.03116300
H	-0.78091900	-2.49435800	-2.29312700
H	-1.95096200	-1.93150900	-1.07554200
N	0.06908600	-1.70410700	-0.56241500
C	-0.06162400	-1.32768800	0.73194100
C	-1.32566100	-1.53844900	1.51447900
H	-1.99073400	-2.21578300	0.97021800
H	-1.05091300	-2.04884700	2.44204500
PC			
C	5.36064800	-0.15749600	0.13615600
C	3.98146300	-0.14668600	0.30479600
C	3.23610200	-1.33476500	0.18525200
C	3.91737300	-2.52562700	-0.10949200
C	5.30190300	-2.53207100	-0.28076100
C	6.02971500	-1.35018000	-0.15683500
H	5.91959300	0.76889900	0.23598000

H	3.45898200	0.77580700	0.52990500
H	3.36931200	-3.45564400	-0.22050700
H	5.80936200	-3.46440500	-0.51214100
H	7.10824600	-1.35549300	-0.28622600
C	1.76391700	-1.31682500	0.33494400
C	0.97464200	-2.59544300	0.38231600
H	1.52776800	-3.36029900	0.93691800
H	0.83543100	-2.99111100	-0.63222800
N	1.21321900	-0.15658400	0.42158500
N	-0.13810000	0.02893000	0.49937100
C	-0.53106800	1.37174200	0.41045400
O	-1.68593500	1.72127400	0.60711300
C	0.50165500	2.41149000	0.06706800
C	0.37036100	3.64289000	0.72094000
C	1.46541800	2.27377100	-0.94167100
C	1.21759400	4.70413500	0.41027500
H	-0.40671000	3.75459300	1.46950100
C	2.29296000	3.34507100	-1.27118200
H	1.56999700	1.33304200	-1.46706600
C	2.18152000	4.55780200	-0.58802000
H	1.11814100	5.64739100	0.93978600
H	3.03044300	3.22909800	-2.06035200
H	2.83847200	5.38630500	-0.83804200
C	-3.37468300	-0.48068600	0.54553000
C	-3.10432800	-0.68762300	-0.81078400
C	-4.04641600	-0.36900800	-1.77278500
C	-5.27835000	0.17052700	-1.37183000
C	-5.53960000	0.37090700	-0.01672700
C	-4.59171100	0.05014900	0.96315800
H	-3.83553000	-0.52734100	-2.82775500
H	-6.02369900	0.43387000	-2.11613000
H	-6.49263600	0.79328200	0.29031400
H	-4.79828800	0.23146600	2.01258900
C	-1.74652800	-1.35201200	-0.95340700
C	-0.89609800	-0.75289300	-2.08145900
H	0.11573400	-1.17154700	-2.09572100
H	-1.36098500	-0.97989500	-3.04652600
H	-0.82149300	0.33334300	-2.00129500
C	-2.00748400	-2.84668200	-1.24751400
H	-2.55814000	-2.92549100	-2.18990400
H	-1.08439900	-3.42633100	-1.35246100
H	-2.62584400	-3.30205800	-0.46887400
C	-2.17801200	-0.38326800	2.69012800
H	-2.25560400	0.71084700	2.71760700
H	-2.96546300	-0.81749800	3.31645700
H	-1.21561200	-0.67567700	3.11335800
N	-2.29459400	-0.88033100	1.33320200
C	-1.12307700	-1.12802500	0.50172300
C	-0.35623800	-2.32822000	1.07382000
H	-0.15429500	-2.12529400	2.13056500
H	-1.00905100	-3.19999200	1.04171400

1a

C	0.66494000	0.75554000	0.00035800
C	0.54755100	-0.64452400	0.00002600
C	1.67985900	-1.43960000	-0.00051400
C	2.94633600	-0.83440100	-0.00112900
C	3.05081600	0.55630900	-0.00134100
C	1.91355000	1.37409700	-0.00080300
H	1.59044200	-2.52323600	-0.00065100
H	3.84191400	-1.44800800	-0.00170900
H	4.03242900	1.02224300	-0.00224900
H	2.01672100	2.45445500	-0.00180300

C	-0.92412200	-1.02655300	0.00074600
C	-1.29806200	-1.81996400	1.26671500
H	-2.37354000	-2.02658200	1.28805800
H	-0.76220100	-2.77566400	1.29080400
H	-1.03867300	-1.25824300	2.16903900
C	-1.29861000	-1.82475400	-1.26188600
H	-0.76279600	-2.78055800	-1.28251400
H	-2.37405500	-2.03162100	-1.28202400
H	-1.03967500	-1.26653000	-2.16649400
C	-0.90825000	2.73770000	0.00169300
H	0.01734700	3.31368600	0.01998300
H	-1.47732600	3.01529000	-0.89564000
H	-1.50617000	3.00688600	0.88243900
N	-0.60792700	1.32872400	0.00216000
C	-1.60536500	0.35143000	-0.00125600
C	-2.92556200	0.58874700	-0.00553400
H	-3.34068100	1.58987800	-0.00796500
H	-3.62673600	-0.23723000	-0.00685600

2a

C	-4.41631000	-1.53593000	-0.44350300
C	-3.13063300	-0.99815100	-0.45390200
C	-2.91968400	0.34396200	-0.09831700
C	-4.02177500	1.12151300	0.29148100
C	-5.30389900	0.58094400	0.29807100
C	-5.50751800	-0.75028500	-0.07300000
H	-4.56347300	-2.57460100	-0.72549100
H	-2.28175100	-1.60863800	-0.73785000
H	-3.87127300	2.14759100	0.61270200
H	-6.14493700	1.19652500	0.60443400
H	-6.50827900	-1.17257200	-0.06312200
C	-1.55727000	0.92054000	-0.11620300
C	-1.25598200	2.22551100	-0.22919400
H	-2.02525200	2.97985200	-0.34577200
H	-0.22160500	2.54692700	-0.25483900
N	-0.52501000	-0.06507700	-0.14362900
N	0.52677300	0.23982400	0.45372500
C	1.52580700	-0.81834200	0.38756800
O	1.23151500	-1.98179700	0.56861600
C	2.90534000	-0.32393500	0.16753400
C	3.92253400	-1.27163600	-0.02224400
C	3.21006200	1.04471500	0.12368100
C	5.22732800	-0.85508500	-0.25916100
H	3.66335700	-2.32424200	0.01845200
C	4.51966000	1.45717600	-0.11349200
H	2.42430300	1.77194500	0.29149100
C	5.52704000	0.51015100	-0.30586100
H	6.01313500	-1.58989800	-0.40754100
H	4.75561900	2.51683600	-0.14318600
H	6.54749600	0.83452700	-0.48962300

2. Pathway-2

RC-4H₂O

C	-4.77259200	-1.75196600	1.05672800
C	-3.49005400	-1.54956800	0.54852400
C	-3.28310400	-0.68293700	-0.53774000
C	-4.39855300	-0.03007300	-1.09146300
C	-5.67754500	-0.23562500	-0.58063400
C	-5.87166900	-1.09765100	0.50005000
H	-4.90832100	-2.43120100	1.89370900
H	-2.65292400	-2.07568600	0.99235900
H	-4.26816200	0.66116000	-1.91800400
H	-6.52220500	0.28505700	-1.02340600

H	-6.86833900	-1.25637500	0.90189500
C	-1.92078800	-0.43148100	-1.06486000
C	-1.68215700	0.12636100	-2.28554700
H	-2.48180500	0.30962000	-2.99121200
H	-0.66782900	0.28085800	-2.62400300
N	-0.88061000	-0.76002900	-0.18158300
N	0.29254700	-0.51305200	-0.60348100
C	1.31184700	-0.88940100	0.32391800
O	1.10640800	-1.23243600	1.48790800
C	2.67524000	-0.83357100	-0.24757900
C	3.76616100	-0.77506700	0.63400300
C	2.89472700	-0.87186700	-1.63357900
C	5.06314400	-0.72339900	0.13685400
H	3.57313700	-0.74650600	1.70049200
C	4.19920400	-0.83669900	-2.12325000
H	2.05221500	-0.98631500	-2.30796000
C	5.28071900	-0.75101800	-1.24448200
H	5.90523900	-0.66409500	0.82040200
H	4.37060200	-0.88284500	-3.19471300
H	6.29482500	-0.71519200	-1.63326300
C	-0.05583700	2.02730200	1.38933100
C	1.04619100	2.43413600	0.62448500
C	2.32383700	2.35780800	1.15635200
C	2.48746100	1.87000000	2.45920100
C	1.37637800	1.48053300	3.21320200
C	0.08229300	1.55921700	2.69179300
H	3.18707500	2.65844800	0.56962200
H	3.48324300	1.79326500	2.88456700
H	1.51769700	1.09941300	4.22002700
H	-0.77280000	1.23570100	3.27457500
C	0.54818600	2.99892600	-0.69348800
C	1.26070300	2.41799500	-1.92089000
H	0.83483800	2.82340900	-2.84518700
H	2.32312800	2.68368400	-1.89826500
H	1.17815000	1.33141800	-1.93298300
C	0.69542200	4.54046800	-0.67791200
H	1.75431000	4.81510400	-0.62416800
H	0.26721300	4.97290800	-1.58844800
H	0.18411400	4.97626700	0.18613700
C	-2.54138700	1.99713600	1.22808900
H	-2.60730300	1.03283700	1.73698300
H	-2.73761500	2.80307800	1.94723700
H	-3.30553400	2.01112200	0.45484100
N	-1.22721700	2.15625300	0.63464600
C	-0.94859100	2.65391400	-0.62863100
C	-1.83264500	2.80153400	-1.64030600
H	-2.89499400	2.63283700	-1.52023600
H	-1.50244100	3.21591000	-2.58466400
O	0.37984900	-2.42450500	-3.04789400
H	0.56873200	-2.89466800	-2.20910800
H	-0.46984600	-1.99658900	-2.86282600
O	-0.88024500	-3.25545300	1.76085700
H	-0.56110400	-2.32973300	1.73185600
H	-0.76361000	-3.52710400	0.82660100
O	1.80558900	-3.95322300	1.71283600
H	0.88017500	-3.91426000	2.05080000
H	2.07137600	-3.01941800	1.80124500
O	0.51144700	-3.93250800	-0.64478100
H	1.18024600	-3.96986000	0.09631900
H	0.46153500	-4.83950500	-0.98272600
TS1-4H₂O			
C	-4.80616800	-1.69413600	1.07565400

C	-3.52185000	-1.49878800	0.57026200
C	-3.30708400	-0.63592500	-0.51825300
C	-4.41963600	0.01762600	-1.07756300
C	-5.70106700	-0.18088800	-0.56898900
C	-5.90184000	-1.03730100	0.51444600
H	-4.94657600	-2.37065100	1.91413200
H	-2.68787200	-2.02777600	1.01678900
H	-4.28840400	0.70077600	-1.91070800
H	-6.54252400	0.34001700	-1.01768700
H	-6.90023900	-1.19127800	0.91382000
C	-1.94079200	-0.39020700	-1.03746100
C	-1.69766500	0.21261400	-2.24596100
H	-2.49287900	0.39137900	-2.95765500
H	-0.68160100	0.32196700	-2.59582000
N	-0.90880300	-0.74022200	-0.17148400
N	0.27403100	-0.50615100	-0.59528100
C	1.28217800	-0.89607800	0.32524400
O	1.08002200	-1.22578200	1.49628900
C	2.64692200	-0.87325900	-0.25083400
C	3.74138200	-0.81468700	0.62565700
C	2.86183400	-0.94401100	-1.63607700
C	5.03787200	-0.79434100	0.12394700
H	3.55217500	-0.76301000	1.69200100
C	4.16513500	-0.93989700	-2.13036700
H	2.01482400	-1.05762100	-2.30535700
C	5.25097700	-0.85375700	-1.25686300
H	5.88289300	-0.73541100	0.80402700
H	4.33230100	-1.01114400	-3.20120700
H	6.26432200	-0.84278500	-1.64920000
C	0.01397700	2.05481300	1.38520100
C	1.10903600	2.43546100	0.59866100
C	2.39178300	2.36221500	1.11823600
C	2.56447500	1.90176400	2.42975900
C	1.45936300	1.53693100	3.20457100
C	0.16031900	1.61405500	2.69548400
H	3.25132100	2.64086700	0.51567100
H	3.56427800	1.82475500	2.84552200
H	1.60937900	1.17546400	4.21726900
H	-0.69100200	1.30741900	3.29265600
C	0.59836300	2.96732400	-0.72752000
C	1.30515800	2.36883200	-1.94930900
H	0.87224700	2.75680100	-2.87787000
H	2.36573700	2.64184200	-1.93766800
H	1.22830300	1.28197600	-1.94134900
C	0.73227500	4.51125600	-0.74397400
H	1.78948800	4.79402700	-0.70509800
H	0.29361000	4.92177000	-1.65966000
H	0.22551300	4.96073000	0.11576000
C	-2.47429100	2.01207700	1.24503100
H	-2.53945400	1.04013800	1.73906200
H	-2.65113300	2.80800900	1.97941500
H	-3.24906100	2.04594800	0.48323500
N	-1.16576900	2.17457000	0.63710700
C	-0.89474700	2.61853300	-0.63983300
C	-1.78679500	2.70367200	-1.66055500
H	-2.85184800	2.58065100	-1.51368500
H	-1.46558500	3.10057600	-2.61545500
O	0.28672700	-2.43863100	-3.02732000
H	0.49187600	-2.91374400	-2.19501200
H	-0.53655500	-1.97776400	-2.80622600
O	-0.92551300	-3.22768800	1.77910500
H	-0.59116300	-2.30729200	1.74216100
H	-0.81515700	-3.50775000	0.84661900

O	1.75534400	-3.94664600	1.73016700
H	0.83071600	-3.90491900	2.06944800
H	2.01729500	-3.01015200	1.80635500
O	0.45491400	-3.94415800	-0.62509700
H	1.12523700	-3.97537800	0.11487700
H	0.39668800	-4.85596300	-0.94827800

IM-4H₂O

C	-5.39479500	0.63081800	-1.44319300
C	-4.11746200	0.70592700	-0.90155000
C	-3.71299000	-0.18367700	0.11579000
C	-4.64007900	-1.14498400	0.55696200
C	-5.92016000	-1.21918700	0.00627800
C	-6.30568600	-0.33201600	-0.99600600
H	-5.68469100	1.33333600	-2.21991700
H	-3.41993900	1.45774100	-1.25284000
H	-4.37184900	-1.85017200	1.33734500
H	-6.61515900	-1.97291000	0.36682300
H	-7.30378200	-0.38454500	-1.42178000
C	-2.33510500	-0.12800400	0.65066100
C	-1.93200600	-0.98829900	1.81849100
H	-2.78871200	-1.23601500	2.44790400
H	-1.21695700	-0.45683400	2.44524700
N	-1.47038500	0.56255100	-0.02254600
N	-0.18569200	0.62279500	0.43980100
C	0.66511000	0.99762200	-0.55141700
O	0.39478800	0.99943800	-1.77744200
C	2.05035800	1.39053400	-0.12255500
C	3.05108600	1.40882000	-1.10547700
C	2.37311400	1.78688100	1.18637000
C	4.35859700	1.76180200	-0.78297200
H	2.77365900	1.13796800	-2.11688100
C	3.68372500	2.14310900	1.50369500
H	1.60198700	1.84900500	1.94792800
C	4.68155400	2.12106500	0.52711200
H	5.12507100	1.76146800	-1.55357300
H	3.92078300	2.45340800	2.51764400
H	5.70043500	2.40128900	0.78128500
C	1.42158300	-2.00657800	-1.13685600
C	2.21430000	-2.11883300	0.00427800
C	3.59483000	-2.04410600	-0.10813600
C	4.14767700	-1.85392200	-1.37833200
C	3.33238400	-1.74699800	-2.51093200
C	1.94117000	-1.81638200	-2.40850600
H	4.23184900	-2.11055300	0.76827600
H	5.22442300	-1.77082200	-1.48560700
H	3.78405800	-1.58387500	-3.48421900
H	1.30570200	-1.68232300	-3.27523300
C	1.31336700	-2.37908600	1.19005400
C	1.55042100	-1.47122200	2.40623600
H	0.86145700	-1.72378900	3.21807100
H	2.57119000	-1.62029400	2.77179000
H	1.41246500	-0.42565400	2.14299900
C	1.45756400	-3.87149700	1.61098400
H	2.47922500	-4.03753100	1.96383400
H	0.77100000	-4.11792600	2.42656500
H	1.27155300	-4.54725600	0.77044600
C	-1.01877800	-1.90365900	-1.73118300
H	-0.96893700	-0.86220000	-2.06288800
H	-0.85041100	-2.59432700	-2.56131900
H	-1.98834100	-2.08954200	-1.27563800
N	0.04927100	-2.10152900	-0.74684800
C	-0.05985100	-2.20613100	0.56146100

C	-1.32894800	-2.34097500	1.32274100
H	-2.07965800	-2.85744900	0.71571900
H	-1.12332500	-2.97036300	2.19415800
O	-0.36750200	1.70380300	3.04382900
H	-0.81950400	2.52041700	2.74989100
H	-0.24196400	1.26732700	2.17194600
O	-1.58577200	3.08450400	-1.60656400
H	-1.17606700	2.20393700	-1.74750200
H	-1.83028000	3.05043800	-0.65958400
O	0.58642200	4.32909000	-0.50321800
H	-0.07575900	3.97639800	-1.15042800
H	1.31548100	3.68900100	-0.52869600
O	-1.35985200	3.70310200	1.27345100
H	-0.51995300	3.94569300	0.79877800
H	-1.79793400	4.55461500	1.42218000

TS2-4H₂O

C	-5.52262800	0.62287200	-1.37228500
C	-4.21396200	0.55254800	-0.90979600
C	-3.84964000	-0.38180600	0.07990700
C	-4.84587200	-1.23960200	0.57617500
C	-6.15691100	-1.16903400	0.10583800
C	-6.50346800	-0.23688400	-0.86971900
H	-5.77861000	1.35742200	-2.13081200
H	-3.46928100	1.23094700	-1.30734800
H	-4.60932100	-1.98108100	1.33107600
H	-6.90610300	-1.84631900	0.50651700
H	-7.52526000	-0.17798500	-1.23403100
C	-2.45060800	-0.46684100	0.55411700
C	-2.03801000	-1.33263700	1.70504800
H	-2.87591000	-1.84099900	2.18076700
H	-1.57103100	-0.70091200	2.46695800
N	-1.53929400	0.17374800	-0.10415900
N	-0.24240600	0.09699000	0.39198400
C	0.61561500	0.73612200	-0.53381500
O	0.34403500	0.85280100	-1.73112800
C	1.87872800	1.36345900	-0.03491800
C	2.94208800	1.46474500	-0.94712100
C	1.99179700	1.97820500	1.22165200
C	4.11859300	2.11428500	-0.59118400
H	2.83154100	1.00942400	-1.92361400
C	3.16984200	2.64160900	1.56682300
H	1.16045600	1.96987500	1.91973200
C	4.23730900	2.70238900	0.67100300
H	4.94215900	2.16415500	-1.29764900
H	3.24402200	3.12226600	2.53793200
H	5.15279700	3.21797200	0.94775200
C	1.80577500	-1.97969200	-1.10388600
C	2.51683100	-1.79622300	0.08973800
C	3.88611600	-1.59230700	0.06263100
C	4.53716400	-1.55161200	-1.17658800
C	3.81626000	-1.73009400	-2.36059900
C	2.43344500	-1.94592100	-2.34405100
H	4.44194800	-1.44209300	0.98355000
H	5.60657900	-1.37005600	-1.21819200
H	4.33211200	-1.68868400	-3.31540500
H	1.87677200	-2.05333800	-3.26819500
C	1.55475300	-2.01040400	1.24051900
C	1.72894700	-1.15322700	2.49099200
H	0.93677400	-1.36815700	3.21569800
H	2.68659400	-1.38967400	2.96727600
H	1.70791000	-0.09127700	2.27270600
C	1.72271800	-3.50713600	1.65201200

H	2.76299100	-3.66759600	1.94842800
H	1.08908100	-3.76618400	2.50585200
H	1.49599000	-4.18157600	0.82135100
C	-0.57307200	-2.20607600	-1.85509600
H	-0.74456700	-1.19583400	-2.23729700
H	-0.23444600	-2.86704700	-2.65696000
H	-1.51105400	-2.59348100	-1.45661300
N	0.43979900	-2.18786600	-0.80721100
C	0.19892000	-1.85710800	0.51189900
C	-1.04080900	-2.38967500	1.20132400
H	-1.56321500	-3.07398000	0.52673100
H	-0.71477700	-2.98824000	2.05438500
O	-0.72927200	1.50872200	2.90168700
H	-1.12358900	2.28229600	2.44697900
H	-0.49518400	0.94976300	2.13466300
O	-1.80270800	2.76223400	-1.72364200
H	-1.39776400	1.87280900	-1.76593200
H	-2.00601100	2.85312300	-0.76882300
O	0.36652400	4.16941600	-0.82760600
H	-0.29534700	3.74961100	-1.43214100
H	1.12917600	3.56997600	-0.85214600
O	-1.47128800	3.51113100	1.02728600
H	-0.66036600	3.80973300	0.53034000
H	-1.93962400	4.33086700	1.24567600

PC-4H₂O

C	-5.43942900	-0.00605700	-1.63907100
C	-4.10535000	-0.18939700	-1.29042800
C	-3.75997300	-0.63415800	-0.00339100
C	-4.78591400	-0.89662100	0.91781000
C	-6.12155500	-0.70989500	0.56617100
C	-6.45350600	-0.26716100	-0.71416200
H	-5.68807500	0.33907600	-2.63846100
H	-3.32284200	0.02260400	-2.00768600
H	-4.54170000	-1.22115900	1.92423000
H	-6.90201000	-0.90793600	1.29537400
H	-7.49464300	-0.12655500	-0.99049300
C	-2.34674400	-0.80492800	0.39006300
C	-1.93441200	-1.73742100	1.48931000
H	-2.74435000	-2.41094000	1.77575800
H	-1.65956500	-1.14684200	2.37162500
N	-1.45014900	-0.14503600	-0.25612000
N	-0.11974300	-0.24639500	0.21833700
C	0.67290000	0.61634800	-0.64835700
O	0.40400400	0.73381400	-1.83252800
C	1.74059700	1.47612200	-0.06733000
C	2.85861100	1.73732600	-0.87544300
C	1.58405700	2.16599200	1.14470300
C	3.83862800	2.62516600	-0.44984000
H	2.95501200	1.21223100	-1.81785000
C	2.56037500	3.07703900	1.55156900
H	0.70107600	2.02236400	1.75922300
C	3.69180400	3.29829100	0.76646500
H	4.71491100	2.79681200	-1.06775200
H	2.42717200	3.61676700	2.48426400
H	4.45222700	4.00145000	1.09429600
C	2.24133500	-1.82378000	-1.00561500
C	2.77343900	-1.47748500	0.24875900
C	4.09316000	-1.08163700	0.37109300
C	4.88935600	-1.00069600	-0.77997400
C	4.35230000	-1.33389800	-2.02540600
C	3.02033200	-1.74612200	-2.15948400
H	4.49986500	-0.81260000	1.34212200

H	5.92079500	-0.67080600	-0.70382200
H	4.97261100	-1.26234200	-2.91459300
H	2.60995500	-1.97869900	-3.13610700
C	1.71550900	-1.76767100	1.29758700
C	1.69631200	-0.88142700	2.54030600
H	0.82142200	-1.10148300	3.16111900
H	2.58651200	-1.08528200	3.14570400
H	1.69001900	0.17870600	2.30901900
C	1.99315800	-3.22544500	1.76258700
H	3.03346900	-3.28544100	2.09467300
H	1.36287300	-3.51577500	2.60976400
H	1.85270900	-3.94254900	0.94949200
C	0.05032900	-2.36429600	-2.03483500
H	-0.17440300	-1.40169100	-2.50569100
H	0.54799900	-3.01973500	-2.75584400
H	-0.89000600	-2.83988200	-1.75014500
N	0.90678000	-2.22458600	-0.86745400
C	0.41043100	-1.71508200	0.40912100
C	-0.75215600	-2.55697000	0.96936300
H	-1.11593400	-3.22424100	0.18460000
H	-0.38053700	-3.20139500	1.76354800
O	-1.09988000	1.17805400	2.71590400
H	-1.68019200	1.77276600	2.19009500
H	-0.67030800	0.65336300	2.01853500
O	-2.07236800	2.26926500	-1.96373000
H	-1.52906000	1.46004300	-1.91967900
H	-2.52570300	2.25476500	-1.09649600
O	-0.47777600	4.02291700	-0.64238500
H	-0.91028700	3.49413100	-1.36209600
H	0.40488700	3.63388900	-0.54067600
O	-2.37470700	2.85324100	0.85498600
H	-1.60569800	3.36842500	0.48316300
H	-3.01215300	3.52492100	1.14005200

2a-4H₂O

C	-4.76548000	1.25750700	-0.01594000
C	-3.47178000	0.75644600	0.12062200
C	-3.21251300	-0.59893400	-0.13654000
C	-4.26697600	-1.42899300	-0.54825700
C	-5.55698500	-0.92257600	-0.68129500
C	-5.81103300	0.42405700	-0.41416000
H	-4.95341000	2.30672100	0.19279200
H	-2.67473600	1.41715200	0.44230000
H	-4.06548500	-2.46900000	-0.78717300
H	-6.36118300	-1.57675100	-1.00581600
H	-6.81603300	0.82159000	-0.52333700
C	-1.85713500	-1.17396500	0.02017000
C	-1.59893500	-2.40366000	0.50368600
H	-2.40569800	-3.04458900	0.84158600
H	-0.57934400	-2.74949500	0.61689100
N	-0.78936600	-0.27865200	-0.28714700
N	0.24008200	-0.82264300	-0.74159700
C	1.28763800	0.12827800	-1.05403800
O	1.02258400	1.19860700	-1.58424500
C	2.65630100	-0.34154300	-0.77509900
C	3.73351900	0.38177200	-1.31371300
C	2.89705500	-1.45453100	0.04531500
C	5.03855700	-0.00640500	-1.03853300
H	3.52996000	1.23202800	-1.95624200
C	4.20864600	-1.82807400	0.32846200
H	2.06617200	-1.98448600	0.49475300
C	5.27649500	-1.11175800	-0.21495100
H	5.87055500	0.54811400	-1.46182400

H	4.39568100	-2.67856500	0.97677600
H	6.29746000	-1.41231200	0.00340000
O	0.81005100	-1.40981700	2.37341800
H	1.09866000	-0.48410900	2.22900400
H	-0.14764200	-1.33270000	2.49392100
O	-0.69458300	2.64318200	0.64252800
H	-0.70500600	1.95369800	-0.04923400
H	-0.29392000	2.16149700	1.39621300
O	1.98885900	3.13893700	0.23317000
H	1.02096100	3.32308400	0.28511900
H	2.04755900	2.65806100	-0.61196200
O	1.33667900	1.35064900	2.11786600
H	1.79481600	1.92055000	1.43549900
H	1.67264900	1.66037700	2.97228000

7. ¹H NMR and ¹³C NMR Spectra

