TFA Mediated Ring-Opening for Evodiamine to Prepare Novel Tryptamine Derivatives

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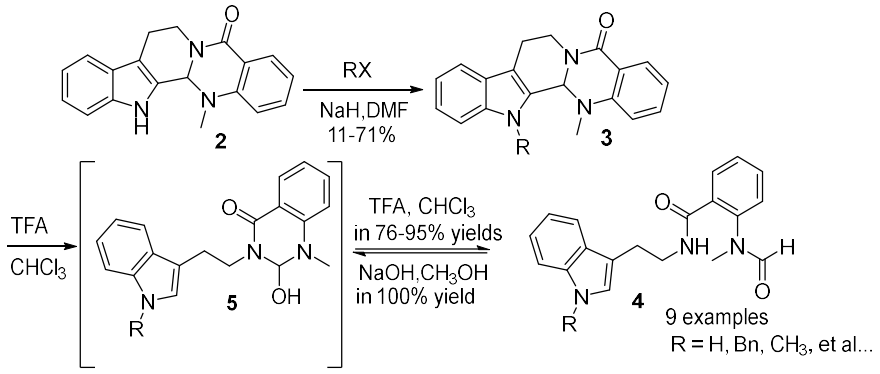
Summary: A convenient feasible protocol was developed for the preparation of novel tryptamine derivatives from evodiamine. After the general alkylation in N-13 and followed by the treatment of TFA in chloroform, a series of tryptamine derivatives **4a-i** were successfully synthesized in a good yield, which were immediately cyclized to form alcohol **5** in the condition of NaOH/methanol.

Graphical Abstract



Keywords: Evodiamine; Ring-opening; Tryptamine; Alkylation; Hydrolysis.

Introduction

Tryptamine is a monoamine alkaloid with an indole ring structure, which is similar in structure to tryptophan. Tryptamine exists in the mammalian brain and functions as a neuromodulator or neurotransmitter. Similar to other trace amines, tryptamine binds to human trace amine related receptor 1 (TAAR1) as an agonist [1-5].

Tryptamine is a common skeleton in a group of compounds called collectively substituted tryptamine. This set includes many biologically active compounds, including neurotransmitters and psychedelics. The diverse pharmacological properties of tryptamine have attracted many medicinal chemists' attention to modify its structure [6-7].

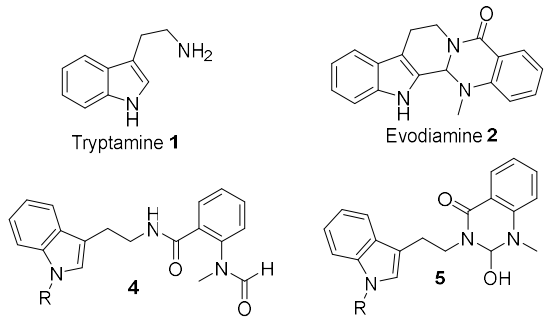


Fig. 1: Structure of Tryptamine, Evodiamine and Derivative **4** and **5.**

There are so many methods to prepare tryptamine derivatives. Among of them, a classical organic reaction for the synthesis of tryptamine is called Abramovitch–Shapiro tryptamine synthesis [8] (Scheme 1).

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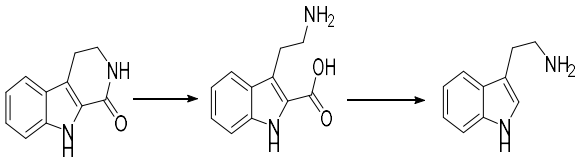


Scheme-1: Abramovitch–Shapiro tryptamine synthesis for Tryptamine.

As a five-cycle fused compound, evodiamine can be easily obtained from natural plant Evodiae fructus. Owing to its pharmacological activities [9-14] (Fig 1), the structural modification of evodiamine has attracted many medicinal chemists' attention. From the structural point of view, evodiamine also contains a tryptamine skeleton, which makes it possible to become a donor of tryptamine derivatives. Considering the similarity in structure, we envision that evodiamine can be converted into tryptamine derivatives under proper reaction conditions. Here we describe our research results.

Experimental

Materials

Melting points were determined in capillary and were uncorrected. ^{1}H and ^{13}C NMR were recorded on a Varian Unity INOVA 400 MHz spectrometer using TMS as an internal standard. MS spectrum (TOF) was measured on an Agilent 1100 Series VS (ES, 4000 V) Mass spectra. All reagents and solvents are reagent grade and were used directly without further purification.

A typical synthetic procedure for **3a (R = Bn)**

A mixture of evodiamine and (100 mg, 0.33 mmol) and NaH (48 mg, 6 equiv.) in DMF (3 ml) was stirred at room temperature for 10 min. To the suspension was added BnCl (0.042 ml, 1.1 equiv.) The reaction was heated to 80℃ for 24 h. After being cooled to room temperature, the solvent was diluted in Ethyl acetate and water. The separated organic layer was dried over $MgSO_4$. The solvent was evaporated completely under reduced pressure to afford the title compound **3a** (71%) as a yellow solid, m.p.143.2-145.1℃, R_f= 0.47 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 6.8 Hz, 4H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 6.6 Hz, 2H), 5.79 (s, 1H), 5.67 (d, *J* = 16.7 Hz, 1H), 5.42 (d, *J* = 16.7 Hz, 1H), 4.88 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.17 (td, *J* = 12.3, 3.9 Hz, 1H), 3.04 (dd, *J* = 15.2, 3.7 Hz, 1H), 2.94-2.88 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.54, 150.73, 137.69, 132.87, 128.85, 128.69, 128.58, 127.38, 126.23, 125.71, 124.20, 124.02, 123.06, 122.91, 119.82, 118.98, 113.67, 109.96, 67.96, 47.11, 39.32, 36.49, 20.35.

Compound (**3b**, R = CH_3, 77%) yellow solid. m.p.180.5-181.3℃, R_f = 0.5 (PE: ethyl acetate = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.24 – 7.15 (m, 3H), 5.96 (s, 1H), 4.90 (dd, *J* = 12.1, 4.2 Hz, 1H), 3.85 (s, 3H), 3.22 – 3.15 (m, 1H), 3.01 (dd, *J* = 14.3, 2.6 Hz, 1H), 2.93 – 2.85 (m, 1H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.66, 150.76, 137.81, 132.87, 128.91, 128.70, 125.51, 123.95, 123.86, 122.84, 122.58, 119.58, 118.90, 112.85, 109.32, 67.96, 39.42, 36.34, 30.02, 20.32.

Compound **3c** (R = C_2H_5, 76%) as a yellow solid, m.p.167.1-168.5℃, R_f = 0.52 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 5.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 5.94 (s, 1H), 4.89 (ddd, *J* = 12.7, 5.0, 1.7 Hz, 1H), 4.40 (dq, *J* = 14.4, 7.2 Hz, 1H), 4.21 (dq, *J* = 14.6, 7.3 Hz, 1H), 3.16 (td, *J* = 12.3, 4.0 Hz, 1H), 3.00 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.93 – 2.81 (m, 1H), 2.39 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.55, 150.88, 136.70, 132.82, 128.92, 128.05, 125.72, 124.15, 124.08, 123.11, 122.52, 119.48, 118.99, 112.89, 109.59, 67.89, 39.30, 38.54, 36.43, 20.35, 15.35.

Compound **3d** (55%) as a yellow solid, m.p.234.6-236.2℃, R_f = 0.56 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.23 – 7.16 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.92 (s, 1H), 4.87 (td, *J* = 14.1, 12.6, 5.4 Hz, 2H), 3.15 (td, *J* = 12.3, 3.9 Hz, 1H), 3.02 – 2.97 (m, 1H), 2.89 – 2.80 (m, 1H), 2.40 (s, 3H), 1.75 (d, *J* = 6.9 Hz, 3H), 1.55 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.52, 150.79, 135.33, 132.78, 128.94, 128.06, 126.60, 124.17, 124.13, 123.14, 122.08, 119.14 (2C), 112.56, 112.35, 68.09, 47.98, 39.17, 36.30, 21.59, 21.54, 20.24.

Compound **3e** (64%) as a yellow solid, m.p.133.8-135.4℃, R_f = 0.59 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.32-7.22 (m, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 6.04-5.89 (m, 2H), 5.11 (d, *J* = 10.3 Hz, 1H), 5.02 (dd, *J* = 16.9, 5.4 Hz, 1H), 4.98-4.81 (m, 3H), 3.19 (td, *J* = 12.3, 3.9 Hz, 1H), 3.03 (d, *J* = 14.9 Hz, 1H), 2.91 (dt, *J* = 14.9, 8.1 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.58, 150.84, 137.30, 133.40, 132.88, 128.92, 128.36, 125.71, 124.19,

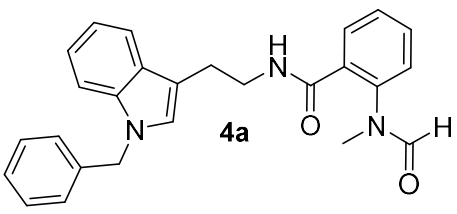
124.07, 123.11, 122.69, 119.71, 118.96, 116.66, 113.29, 109.94, 67.89, 46.11, 39.34, 36.58, 20.34.

Compound **3f** (69%) as a yellow solid, m.p.176.1-178.5℃, R_f = 0.42 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 8.2, 6.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.22 – 7.16 (m, 3H), 6.01 (s, 1H), 5.16 (dd, *J* = 18.1, 2.5 Hz, 1H), 4.99 (dd, *J* = 18.1, 2.5 Hz, 1H), 4.88 (ddd, *J* = 12.8, 5.1, 1.8 Hz, 1H), 3.19 (ddd, *J* = 12.8, 11.7, 4.1 Hz, 1H), 3.02 – 2.96 (m, 1H), 2.92 – 2.85 (m, 1H), 2.41 (s, 3H), 2.25 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.56, 150.72, 136.94, 132.93, 128.88, 127.83, 126.01, 124.38, 124.09, 123.33, 123.05, 120.21, 119.09, 113.93, 109.80, 78.31, 72.71, 67.81, 39.18, 36.81, 33.09, 20.21.

Compound **3g** (67%) as a yellow solid, m.p.215.4-218.7℃, R_f = 0.32 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.38 (dt, *J* = 15.1, 8.2 Hz, 2H), 7.25 (dd, *J* = 12.4, 7.2 Hz, 3H), 5.96 (s, 1H), 5.30 (d, *J* = 18.0 Hz, 1H), 5.14 (d, *J* = 18.0 Hz, 1H), 4.89 (dd, *J* = 13.0, 4.9 Hz, 1H), 4.32 (s, 1H), 3.20 (td, *J* = 12.4, 4.2 Hz, 1H), 2.99 (dd, *J* = 15.6, 4.0 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.53, 150.46, 136.86, 133.28, 128.94, 126.26, 125.11, 124.08, 124.03, 123.68, 121.24, 119.56, 115.47, 114.50, 111.39, 109.04, 48.72, 39.06, 37.04, 31.76, 20.05.

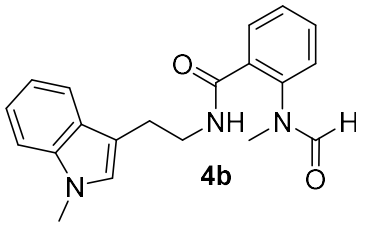
Compound **3h** (36%) as a yellow solid, m.p.105.1-107.6℃, R_f = 0.8 (PE: EA = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.50 (td, *J* = 7.6, 1.7 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.32-7.23 (m, 2H), 7.18 (dt, *J* = 13.6, 7.0 Hz, 2H), 5.97 (s, 1H), 4.91 (ddd, *J* = 12.7, 5.1, 1.8 Hz, 1H), 4.35 (dt, *J* = 15.8, 7.8 Hz, 1H), 4.17 (dt, *J* = 14.8, 7.2 Hz, 1H), 3.19 (td, *J* = 12.2, 4.0 Hz, 1H), 3.03 (dd, *J* = 15.1, 3.7 Hz, 1H), 2.94-2.85 (m, 1H), 2.40 (s, 3H), 1.87-1.79 (m, 2H), 1.35-1.23 (m, 8H), 0.88-0.81 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.58, 150.92, 137.11, 132.87, 128.94, 128.29, 125.66, 124.15, 124.09, 123.04, 122.49, 119.45, 118.95, 112.88, 109.80, 68.05, 43.97, 39.33, 36.44, 31.72, 30.14, 28.97, 27.13, 22.58, 20.38, 14.04.

A typical synthetic procedure for N-(2-(1-benzyl-1H-indol-3-yl) ethyl)-2-(N-methylformamido) benzamide **(4a, R = Bn)**



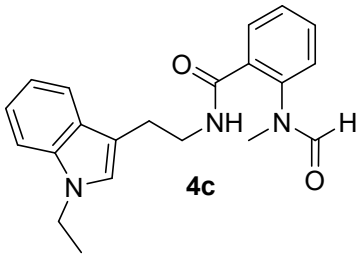
4a

A mixture of compound (**3a**, 75 mg, 0.19 mmol) and TFA (0.2 ml, 14 **equiv**.) in $CHCl_3$ (2 ml) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography to give the desired product **4a** (93%) as a yellow solid. M.p.112.1-113.8℃, R_f = 0.32 (CH_2Cl_2: CH_3OH = 15:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.95 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.19 – 8.13 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.30 – 7.23 (m, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 7.11 – 7.06 (m, 1H), 7.01 (dd, *J* = 12.9, 5.2 Hz, 1H), 5.35 (s, 1H), 4.33 (d, *J* = 7.7 Hz, 2H), 4.01 (s, 1H), 3.25 – 3.17 (m, 1H), 2.69 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.23, 154.33, 138.66, 138.43, 137.30, 136.50, 131.34, 130.44, 129.96, 129.31, 128.94, 128.35, 127.89, 127.74, 127.42, 122.00, 120.09, 119.33, 118.96, 118.93, 110.75, 109.74, 49.48, 49.38, 42.05, 24.43.



4b

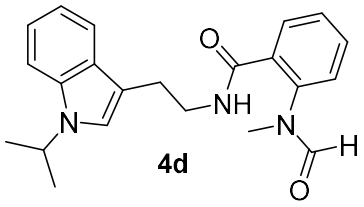
4b (80.3 mg, 95%) as a yellow solid, M.p.200.8-201.2℃, R_f = 0.3 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.96 (d, *J* = 3.6 Hz, 1H), 8.37 (dd, *J* = 8.1, 3.6 Hz, 1H), 8.18 (s, 1H), 8.02 (dd, *J* = 8.6, 3.1 Hz, 1H), 7.91 – 7.84 (m, 1H), 7.63 (dd, *J* = 8.0, 3.2 Hz, 1H), 7.39 (dd, *J* = 8.3, 3.2 Hz, 1H), 7.25 (d, *J* = 3.1 Hz, 1H), 7.18 – 7.10 (m, 1H), 7.04 – 6.95 (m, 1H), 4.30 (s, 1H), 4.02 (d, *J* = 3.2 Hz, 1H), 3.73 (d, *J* = 3.0 Hz, 1H), 3.18 (dd, *J* = 14.7, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.26, 154.31, 138.45, 137.29, 137.10, 130.41, 128.34, 128.31, 127.60, 121.80, 120.11, 119.09, 118.93, 118.72, 110.27, 109.05, 49.65, 40.57, 32.75, 24.40.



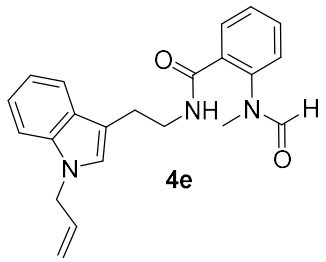
4c

4c (92%) as a yellow solid, M.p.172.8-174.3℃, R_f = 0.31(CH_2Cl_2 : CH_3OH = 15 : 1).^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.96 (s, 1H), 8.37 (t, *J* = 7.7 Hz, 1H), 8.16 (t, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.30 (s, 1H), 7.12 (t, *J* = 7.6

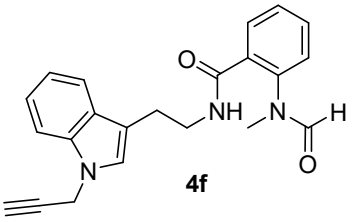
Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.20 – 4.10 (m, 1H), 4.01 (s, 1H), 3.23 – 3.11 (m, 1H), 1.30 (q, *J* = 7.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 158.24, 154.31, 138.45, 137.28, 136.10, 130.40, 128.30, 127.72, 126.69, 121.74, 120.11, 119.05, 118.93, 118.87, 110.25, 109.23, 49.59, 40.57, 40.55, 24.46, 15.87.



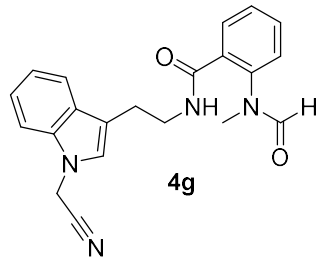
4d (87%) as a yellow solid, M.p.195.1-196.4℃, R_f = 0.38 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 9.94 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.16 (t, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.39 (s, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.69 (p, *J* = 6.6 Hz, 1H), 4.36 – 4.26 (m, 2H), 4.01 (s, 3H), 3.19 (t, *J* = 7.9 Hz, 2H), 1.39 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 158.24, 154.28, 138.46, 137.30, 135.94, 128.32, 127.63, 123.37, 121.68, 120.14, 119.12, 118.93, 118.87, 110.40, 109.49, 49.54, 46.74, 40.60, 24.58, 22.90.



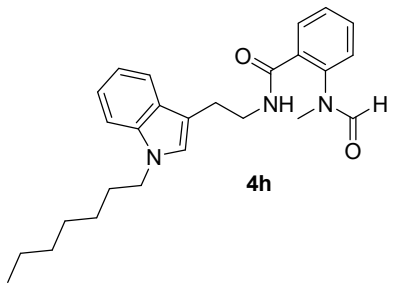
4e (91%) as a yellow solid, M.p.162.7-163.6℃, R_f = 0.33 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 9.94 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.20 – 8.13 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.02 – 5.87 (m, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.95 (d, *J* = 17.1 Hz, 1H), 4.76 (s, 1H), 4.31 (d, *J* = 7.8 Hz, 2H), 4.02 (s, 3H), 3.20 (d, *J* = 8.0 Hz, 1H), 2.73 (s, 1H).^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 158.22, 154.30, 138.43, 137.30, 136.50, 134.87, 130.42, 128.34, 127.75, 127.39, 121.89, 120.10, 119.25, 118.94, 118.88, 116.97, 110.63, 109.53, 49.53, 48.31, 42.47, 24.41.



4f (85%) as a yellow solid, M.p.171.6-173.1℃, R_f = 0.29 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 9.96 (d, *J* = 6.2 Hz, 1H), 8.38 (s, 1H), 8.18 (s, 1H), 8.03 (t, *J* = 7.4 Hz, 1H), 7.89 (s, 1H), 7.72 – 7.65 (m, 1H), 7.53 – 7.46 (m, 1H), 7.33 (d, *J* = 5.7 Hz, 1H), 7.18 (dd, *J* = 13.8, 6.1 Hz, 1H), 7.06 (dd, *J* = 13.5, 5.8 Hz, 1H), 5.04 (d, *J* = 7.9 Hz, 1H), 4.32 (s, 1H), 4.03 (d, *J* = 6.4 Hz, 1H), 3.37 (s, 1H), 3.17 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 158.25, 154.35, 138.44, 137.31, 136.28, 130.43, 128.35, 127.96, 126.97, 122.19, 120.13, 119.69, 119.02, 118.95, 110.66, 110.21, 79.75, 75.89, 49.46, 40.65, 35.39, 24.38.

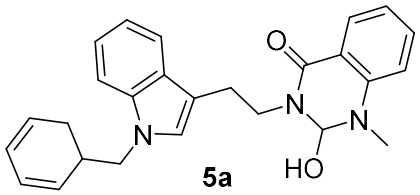


4g (77%) as a white solid, M.p.161.4-162.8℃, R_f = 0.37 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 10.02 (s, 1H), 8.37 (d, *J* = 9.5 Hz, 1H), 8.16 (t, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.51 (s, 2H), 4.36 – 4.28 (m, 2H), 4.04 (s, 3H), 3.24 – 3.17 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 158.27, 154.44, 138.47, 137.31, 136.46, 130.43, 128.34, 128.16, 127.15, 122.92, 120.46, 120.12, 119.35, 118.96, 117.07, 111.81, 110.43, 49.26, 40.63, 34.15, 24.25.



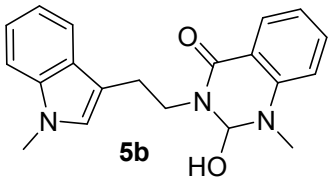
4h (93%) as a yellow solid, M.p.132.8-133.6℃, R_f = 0.48 (CH_2Cl_2 : CH_3OH = 15 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.98 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.16 (t, *J* = 7.9 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.28 (s, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 4.34 – 4.25 (m, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 4.02 (s, 3H), 3.18 (dd, *J* = 9.5, 6.4 Hz, 2H), 2.71 (s, 1H), 1.67 (p, *J* = 7.1 Hz, 2H), 1.19 (ddd, *J* = 14.0, 8.9, 3.9 Hz, 8H), 0.80 (t, *J* = 6.8 Hz, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.24, 154.35, 138.45, 137.29, 136.45, 130.40, 128.31, 127.64, 127.29, 121.73, 120.11, 119.01, 118.94, 118.85, 110.33, 109.11, 49.53, 45.72, 40.59, 31.61, 30.30, 28.72, 26.64, 24.44, 22.44, 14.34.

A typical synthetic procedure for 3-(2-(1-(cyclohexa-2, 4-dien-1-ylmethyl)-1H-indol-3-yl) ethyl)-2-hydroxy-1-methyl-2, 3-dihydroquinazolin-4(1H)-one (**5a**, R = Bn)



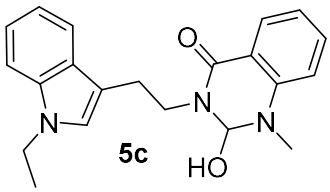
5a

To a solution of compound (**4a**, 100 mg, 0.24 mmol) in methanol (2 ml) was added NaOH (19.5 mg, 2 equiv.). The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was neutralized by diluted HCl (1N) and extracted with DCM. The separated organic layer was dried over $MgSO_4$. The solvent was evaporated completely under reduced pressure to afford the compound **5a** (100%) as a white solid, M.p.43.2-45.6℃, R_f = 0.32 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 and 7.79 (s, 1H), 7.63 (dd, *J* = 13.6, 7.8 Hz, 1H), 7.44 (q, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 4.6 Hz, 1H), 7.23 – 7.20 (m, 2H), 7.20 – 6.99 (m, 6H), 6.39 and 5.98 (s, 1H), 5.27 (d, *J* = 7.3 Hz, 2H), 3.74 (dq, *J* = 13.4, 6.5 Hz, 2H), 3.10 (s, 2H), 3.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.61, 166.91, 163.18, 162.56, 139.29, 137.56, 137.53, 137.05, 136.87, 136.71, 135.87, 133.81, 131.27, 131.20, 129.21, 128.80, 128.71, 128.48, 127.93, 127.85, 127.75, 127.57, 127.55, 127.41, 126.90, 126.79, 126.44, 126.41, 122.04, 121.92, 119.26, 119.16, 118.97, 118.90, 111.79, 111.59, 109.85, 109.75, 49.94, 49.82, 40.08, 39.88, 38.07, 33.64, 25.10, 25.02. HRMS (ESI-ToF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{25}N_3O_2Na$ 434.4948; Found 434.1845.



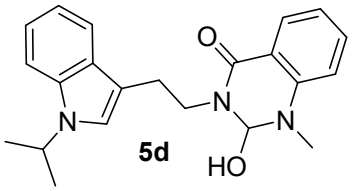
5b

2-hydroxy-1-methyl-3-(2-(1-methyl-1H-indol-3-yl)ethyl)-2,3-dihydroquinazolin-4(1H)-one (**5b**, 100%), M.p.40.5-43.5℃, R_f = 0.22 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 and 7.66 (s, 1H), 7.56 (dt, *J* = 14.4, 7.2 Hz, 1H), 7.47 (dd, *J* = 10.1, 5.8 Hz, 1H), 7.41 (dd, *J* = 13.9, 6.3 Hz, 1H), 7.34-7.25 (m, 1H), 7.21-7.16 (m, 1H), 7.11-7.02 (m, 1H), 6.96-6.90 (m, 1H), 6.37 and 6.04 (s, 1H), 3.77-3.66 (m, 1H), 3.10 (s, 1H), 3.04-2.96 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.56, 166.92, 163.15, 162.56, 139.22, 137.13, 137.06, 136.97, 135.78, 133.78, 131.26, 131.21, 129.28, 128.87, 128.48, 127.91, 127.84, 127.52, 127.34, 127.13, 121.76, 121.69, 118.93, 118.87, 118.83, 118.73, 110.92, 110.72, 109.36, 109.24, 40.18, 39.80, 38.01, 33.61, 32.64, 32.62, 24.99, 24.87. HRMS (ESI-ToF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{21}N_3O_2Na$ 358.3968; Found 358.1484.



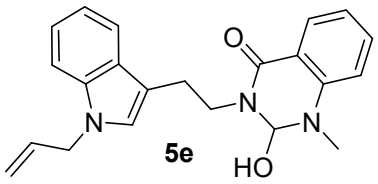
5c

3-(2-(1-ethyl-1H-indol-3-yl)ethyl)-2-hydroxy-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**5c**, 100%) as a yellow solid, M.p.39.4-41.7℃, R_f = 0.25 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 and 7.72 (s, 1H), 7.58 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.52 -7.38 (m, 2H), 7.35-7.27 (m, 2H), 7.21-7.16 (m, 1H), 7.12-7.03 (m, 2H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.37 and 5.91 (s, 1H), 4.15-4.08 (m, 2H), 3.78-3.70 (m, 2H), 3.13 (s, 2H), 3.07-2.96 (m, 3H), 1.42 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.58, 166.89, 163.21, 162.55, 139.24, 136.97, 136.17, 136.06, 135.84, 133.78, 131.31, 131.21, 129.26, 128.87, 128.50, 127.93, 127.84, 127.64, 127.38, 125.44, 125.30, 121.64, 121.55, 118.95, 118.91, 118.85, 118.83, 111.02, 110.78, 109.44, 109.29, 40.77, 40.17, 39.84, 38.04, 33.67, 29.67, 25.09, 24.97, 15.45, 15.41. HRMS (ESI-ToF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{23}N_3O_2H$ 350.4420; Found 350.1823.



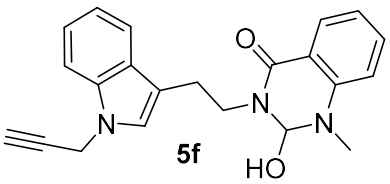
5d

2-hydroxy-3-(2-(1-isopropyl-1H-indol-3-yl)ethyl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**5d**, 100%) as a yellow solid, M.p.47.6-49.5℃, R_f = 0.30 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 and 7.67 (s, 1H), 7.56 (dd, *J* = 14.9, 7.9 Hz, 1H), 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.16 (q, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.51 and 6.38 (s, 1H), 4.55-4.61 (m, 1H), 3.73 – 3.64 (m, 2H), 3.11 (s, 2H), 2.99 (dd, *J* = 12.6, 6.0 Hz, 3H), 1.45 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.56, 167.13, 163.16, 162.56, 139.31, 137.08, 135.92, 135.83, 135.76, 134.03, 131.16, 131.15, 129.01, 128.79, 128.38, 127.85, 127.79, 127.66, 127.32, 121.97, 121.87, 121.42, 121.39, 118.93, 118.87, 118.84, 111.18, 111.13, 109.59, 109.52, 46.91, 46.88, 40.34, 39.99, 38.01, 33.59, 25.30, 25.12, 22.73(2C). HRMS (ESI-ToF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{25}N_3O_2H$ 364.4690; Found 364.1984.



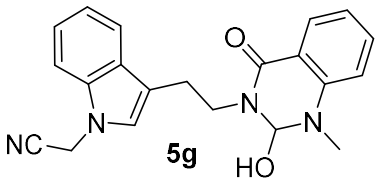
5e

3-(2-(1-allyl-1H-indol-3-yl)ethyl)-2-hydroxy-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**5e**, 100%) as a yellow solid, M.p.35.9-37.7℃, R_f = 0.22 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 and 7.69 (s, 1H), 7.56 (dd, *J* = 15.5, 7.9 Hz, 1H), 7.45-7.34 (dt, *J* = 16.1, 7.8 Hz, 2H), 7.30-7.21 (m, 2H), 7.15 (q, *J* = 7.2 Hz, 1H), 7.05 (dt, *J* = 10.4, 7.6 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.41 and 6.15 (s, 1H), 5.92 (ddq, *J* = 15.7, 10.3, 5.3, 4.6 Hz, 1H), 5.18 – 4.95 (m, 2H), 4.64 (dt, *J* = 5.3, 1.7 Hz, 2H), 3.69 (dtd, *J* = 9.7, 6.2, 2.4 Hz, 2H), 3.09 (s, 2H), 3.05 – 2.92 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.57, 167.01, 163.15, 162.57, 139.25, 137.01, 136.53, 136.44, 135.74, 133.84, 133.49, 131.22, 131.20, 129.17, 128.80, 128.44, 127.93, 127.86, 127.82, 127.74, 127.33, 126.08, 126.00, 121.78, 121.72, 119.08, 119.03, 118.92, 117.28, 117.18, 111.44, 111.25, 109.74, 109.64, 48.71, 48.64, 40.16, 39.88, 38.05, 33.62, 25.05, 24.94. HRMS (ESI-ToF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{23}N_3O_2H$ 362.4530; Found 362.1825.



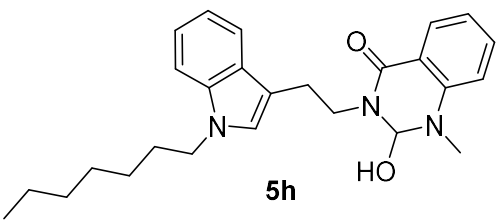
5f

2-hydroxy-1-methyl-3-(2-(1-(prop-2-yn-1-yl)-1H-indol-3-yl)ethyl)-2,3-dihydroquinazolin-4(1H)-one (**5f**, 100%) as a white solid, M.p.119.4-120.3℃, R_f = 0.26 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 and 7.72 (s, 1H), 7.58 (dd, *J* = 15.9, 7.9 Hz, 1H), 7.47 (ddd, *J* = 11.6, 7.6, 1.6 Hz, 1H), 7.41-7.33 (m, 2H), 7.30 (qd, *J* = 7.7, 1.2 Hz, 1H), 7.25-7.20 (m, 1H), 7.15-7.01 (m, 3H), 6.38 and 6.00 (s, 1H), 4.82 (dd, *J* = 10.8, 2.5 Hz, 2H), 3.72 (dq, *J* = 12.4, 6.3 Hz, 2H), 3.10 (s, 2H), 3.05-2.97 (m, 3H), 2.34 (q, *J* = 2.7 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.56, 166.91, 163.22, 162.56, 139.24, 136.99, 136.28, 136.17, 133.78, 131.28, 131.23, 129.30, 128.90, 128.49, 128.00, 127.92, 127.82, 127.36, 125.59, 125.49, 122.21, 122.14, 119.61, 119.55, 119.12, 119.02, 112.22, 111.93, 109.57, 109.46, 77.86, 73.40, 39.95, 39.68, 38.07, 35.68, 35.64, 33.69, 25.00, 24.90. HRMS (ESI-ToF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{21}N_3O_2H$ 360.4370; Found 360.1671.



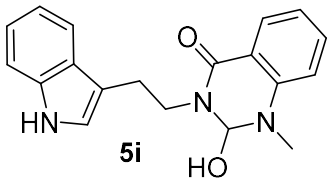
5g

2-(3-(2-(2-hydroxy-1-methyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl)-1H-indol-1-yl)acetonitrile (**5g**, 100%) as a brown solid, M.p. 65.8-68.2℃, R_f = 0.16 (PE: EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 and 7.74 (s, 1H), 7.57 (dd, *J* = 16.7, 7.9 Hz, 1H), 7.47-7.35 (m, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 4.0 Hz, 1H), 7.14 (dd, *J* = 16.7, 9.2 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 13.0 Hz, 1H), 6.44 and 6.18 (s, 1H), 4.94 (d, *J* = 36.2 Hz, 2H), 3.77-3.62 (m, 1H), 3.04 (d, *J* = 4.1 Hz, 3H), 3.00-2.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.67, 167.10, 163.17, 162.74, 139.04, 137.03, 136.27, 136.16, 135.66, 133.74, 131.33, 129.30, 128.73, 128.53, 128.20, 128.05, 127.82, 127.38, 125.51, 125.48, 123.10, 123.05, 120.46, 119.44, 119.34, 114.80, 114.62, 114.11, 113.80, 109.10, 108.97, 60.39, 39.53, 39.43, 38.20, 34.06, 33.72, 24.81, 24.71. HRMS (ESI-ToF) *m/z*: $[M+CH_3OH+Na+H]^+$ Calcd for $C_{23}H_{25}N_4O_5Na$ 416.1824; Found 416.1542.



5h

3-(2-(1-heptyl-1H-indol-3-yl)ethyl)-2-hydroxy-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**5h**, 100%) as a white solid, M.p. 84.1-85.8℃, R_f = 0.3 (Ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 and 7.75 (s, 1H), 7.59 (dd, *J* = 15.0, 7.9 Hz, 1H), 7.44 (dt, *J* = 17.2, 7.6 Hz, 2H), 7.36-7.27 (m, 2H), 7.19 (dd, *J* = 13.6, 6.6 Hz, 1H), 7.16-7.03 (m, 2H), 6.99 (d, *J* = 9.9 Hz, 1H), 6.40 and 6.05 (s, 1H), 4.05 (dd, *J* = 13.3, 6.6 Hz, 2H), 3.74 (dt, *J* = 12.1, 6.1 Hz, 2H), 3.24-3.10 (m, 2H), 3.09-2.99 (m, 3H), 1.78 (dd, *J* = 13.6, 6.4 Hz, 2H), 1.41-1.13 (m, 8H), 0.99 – 0.75 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.57, 166.93, 163.17, 162.53, 139.32, 137.07, 136.46, 136.38, 135.87, 133.92, 131.25, 131.18, 129.17, 128.82, 128.45, 127.88, 127.86, 127.62, 127.39, 126.12, 126.01, 121.59, 121.51, 118.91, 118.84, 118.83, 118.77, 110.92, 110.69, 109.55, 109.42, 46.24, 40.23, 39.91, 38.03, 31.67, 30.27, 28.91, 26.99, 25.13, 25.01, 22.56, 14.04. HRMS (ESI-ToF) *m/z*: 442.24 $[M+Na]^+$ Calcd for $C_{26}H_{33}N_3O_2Na$ 442.5588; Found 442.2457.

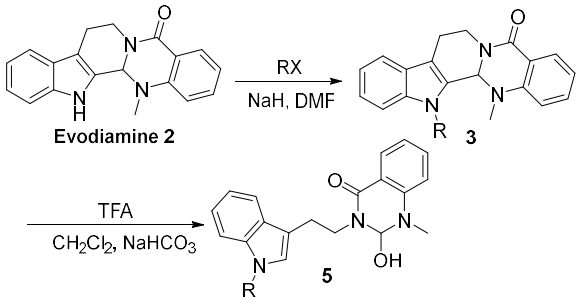


5i

3-(2-(1H-indol-3-yl)ethyl)-2-hydroxy-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**5i**, 100%) as a white solid, M.p. 95-98.4℃, R_f = 0.23 (PE: EA = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.31 and 8.25 (s, 1H), 8.11 and 7.70 (s, 1H), 7.59 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.52 – 7.39 (m, 2H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.18 (q, *J* = 7.8, 6.6 Hz, 1H), 7.08 (dd, *J* = 13.8, 7.6 Hz, 3H), 6.37 (s, 1H), 3.76 (dq, *J* = 19.1, 6.3 Hz, 2H), 3.10 (s, 2H), 3.03 (q, *J* = 6.1, 5.6 Hz, 2H), 2.99 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.62, 166.98, 163.32, 162.69, 139.19, 136.96, 136.45, 136.34, 133.82, 131.33, 131.29, 129.24, 128.93, 128.03, 127.86, 127.46, 127.07, 122.56, 122.45, 122.17, 122.09, 119.42, 119.37, 118.70, 118.57, 112.42, 112.11, 111.38, 111.25, 39.87, 39.60, 38.11, 33.73, 25.04, 24.92.

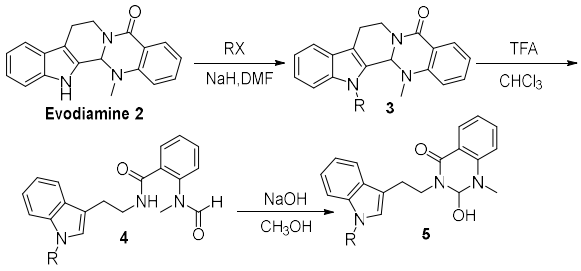
Results and Discussion

Evodiamine can be easily converted into tryptamine derivatives **5** according to our previous synthetic work [15], which is outlined in Scheme 1. Thus, evodiamine was reacted with alkyl halides upon treatment of sodium hydride to give N-13 substituted evodiamine **3** in good yield. When compound **3** was treated with TFA, ring C was smoothly opened and led to the formation of urea alcohol **5** in reasonable yield.



Scheme-1: Previous synthetic route for derivatives **5.**

However, when we investigate this rearrangement reaction again, an interesting thing occurred in the second step. It was found that the use of base or not will lead to different reaction results in the workup condition. If no base was used, a novel full ring-opening aldehyde **4** will be obtained, which is quite different from our previous reported compound **5** (Scheme 2). Compound **5** is actually difficult to synthesize by the traditional procedure from the starting material of tryptamine because of its unique urea alcohol structure.



Scheme-2: Synthetic route for the new tryptamine derivatives **4** and **5.**

The structure of ring opening of tryptamine derivatives **4** was firstly identified by ^{1}HNMR, ^{13}CNMR and MS spectrum. Both of ^{1}HNMR and ^{13}CNMR clearly indicate the existence of a pair of isomers. From the structure to see, they are probably rotamers due to the two amide functions. But many of the ^{1}H and ^{13}CNMRs indicate a single set of resonances indicating a favoured rotamer in solution.

The exact structure of key intermediate tryptamine aldehyde **4** was determined by X-ray. The

product of **4h** (R = n-heptyl) was selected as an example, which was recrystallized from dichloromethane and methanol to give colorless crystals suitable for single-crystal X-ray diffraction. A suitable crystal was selected and recorded on a Super Nova, Dual, Cu at zero, Atlas S2 diffractometer. The crystal was kept at 149.99(10) K during data collection. Crystal Data for $C_{26}H_{33}N_3O_2$ (M = 419.55 g/mol) : triclinic, space group P-1, a = 5.07250(10) Å, b = 17.4363(8) Å, c = 27.5310(9) Å, α = 74.714(3), β = 86.781(2), γ = 82.804(3), V = 2329.67(14)Å^3, Z = 4, T = 149.99(10) K, μ(Mo Kα) = 0.599 mm^{-1}, ρcalc = 1.196g/cm^3, reflections measured = 15997, ($5.29 \leq 2\Theta \leq 147.588$), Independent reflections = 9125 (R_{int} = 0.0395, R_{sigma} = 0.0569) which were used in all calculations. The final R_1 was 0.0669 ($I > 2\sigma$ (I) and wR_2 was 0.1766 (all data). And the structure of 4h was shown in Fig 2.

The ring opening reaction of N13 benzyl-substituted evodiamine was optimized by different reaction conditions, including different acids, solvents and times. The results were summarized in table 1.

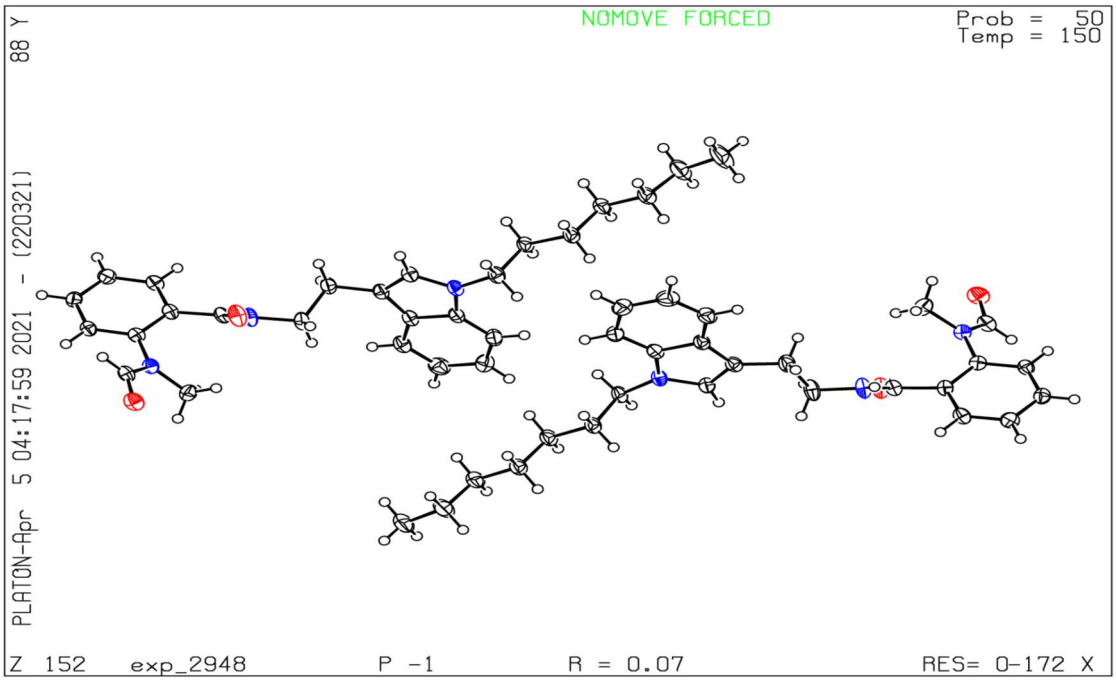
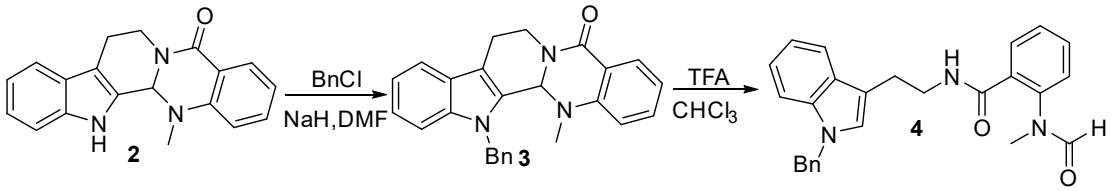


Fig. 2: X-ray for Compound **4h.**

Table-1: Process optimization of ring opening reaction.



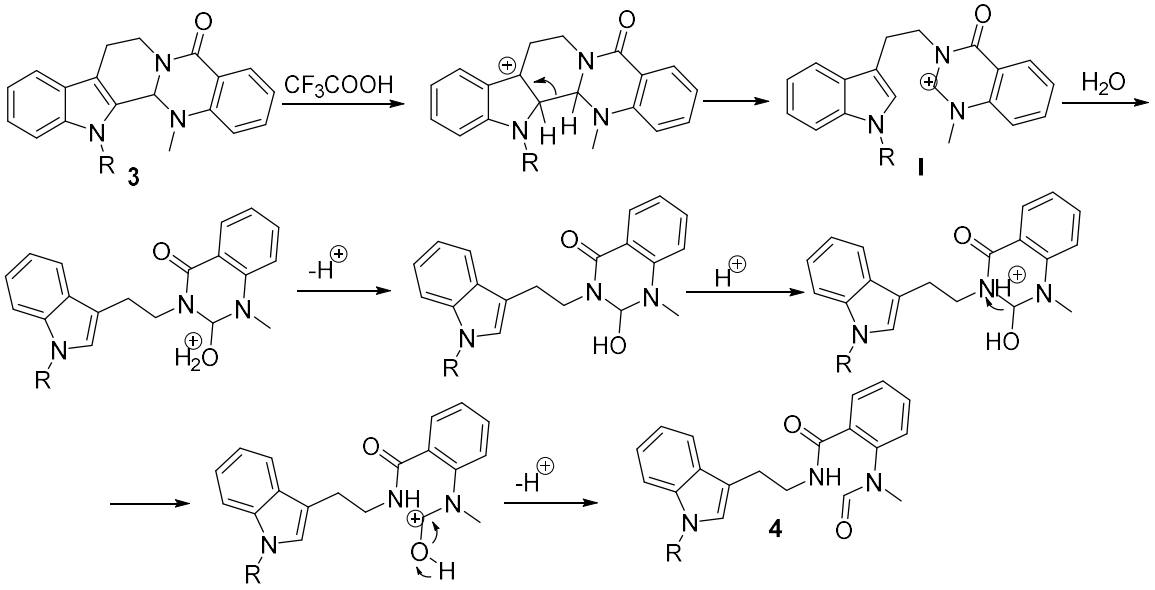
Entry	Acid	Solvent	Temp/time	Yield	SM recovered
1	1N HCl (excess)	H_2O	Reflux/12h	-	100%
2	Conc. HCl (excess)	H_2O	Reflux/12h	-	100%
3	Conc. H_2SO_4	methanol	Reflux/12h	-	100%
4	TFA (3equ.)	DCM	0℃/12 h	8%	67%
5	TFA (3equ.)	DCM	Rt/12 h	15%	58%
6	TFA (7equ.)	DCM	Rt/24 h	32%	42%
7	TFA (14equ.)	DCM	Rt/24 h	56%	18%
8	TFA (14equ.)	DCM	Reflux/24 h	54%	15%
9	TFA (21equ.)	DCM	Reflux/24 h	52%	12%
10	TFA (14equ.)	$CHCl_3$	Reflux/24h	93%	trace

It is interesting to find that both of hydrochloric acid and sulphuric acid cannot degrade

evodiamine at any concentration but only TFA can work. Meanwhile, an excessive amount of TFA in DCM would cause the ring-opening reaction of N13 evodiamine. The yield can be up to 56%. When chloroform was used at reflux, the yield can be increased to 93%.

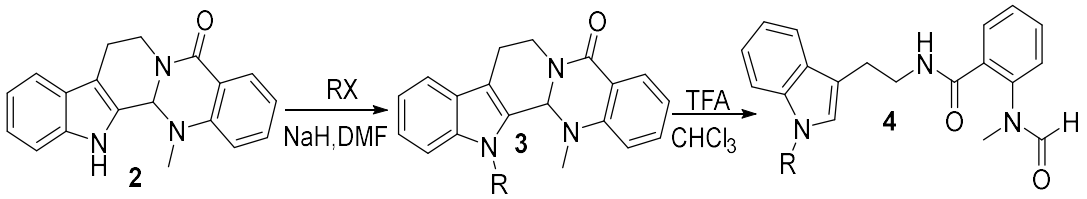
This particular reaction result drives us to make extensive research on its mechanism. Considering of the electrophilicity of indole moiety, a possible reaction mechanism was proposed to explain the formation of the product (Scheme 3).

Based on this intriguing result, we expand the reaction substrates. Luckily, all of these substrates smoothly gave the designed ring-opened product **4a-h** in good yield respectively. It was found that several functional groups, such as double bond (C=C), triple bond and nitrile (CN) can tolerate the reaction. Meanwhile, the ring opening reaction of N13-unsubstituted evodiamine (**2**) proceeds also well to give the desired product. The yield of this reaction was range from 76% to 95%. Table 2 summarized all of results for this reaction.



Scheme-3: Proposed TFA Mediated Mechanism for Tryptamine Derivatives **4.**

Table-2: Structure characterization of compounds **3a-h** and **4a-h.**



Entry	R	Alkylation condition	Yield Product 3	Degradation condition	Yield Product 4
a	Bn	NaH/DMF/80℃	67%	TFA/$CHCl_3$	93%
b	CH_3	NaH/DMF/80℃	77%	TFA/$CHCl_3$	95%
c	CH_2CH_3	NaH/DMF/80℃	76%	TFA/$CHCl_3$	92%
d	$CH(CH_3)_2$	NaH/DMF/80℃	52%	TFA/$CHCl_3$	87%
e	allyl	NaH/DMF/80℃	55%	TFA/$CHCl_3$	91%
f		NaH/DMF/80℃	71%	TFA/$CHCl_3$	85%
g	CH_2CN	NaH/DMF/80℃	60%	TFA/$CHCl_3$	77%
h	n-heptyl	NaH/DMF/80℃	36%	TFA/$CHCl_3$	93%
i	H			TFA/$CHCl_3$	76%

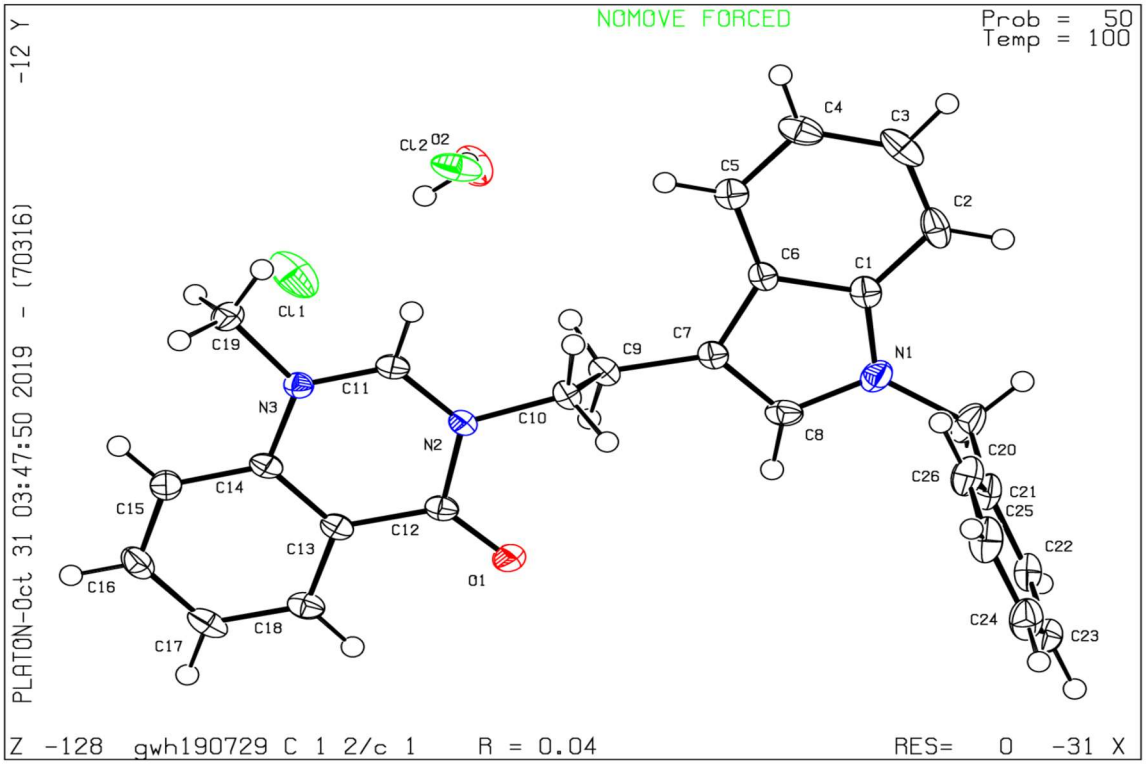
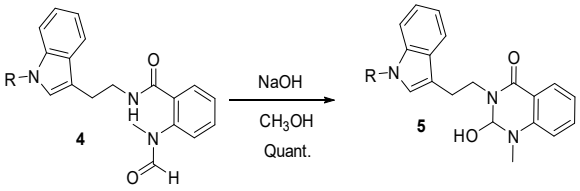


Fig. 3: X-ray for Compound **5a (R = Bn).**

It is interesting to find that the aldehyde **4** can be easily cyclized to form cyclic alcohol **5** in a quantitative yield in the condition of NaOH/CH_3OH (Scheme 4).

The exact structure of cyclized product **5** was determined by X-ray. The product of **5a** (R = benzyl) was selected as an example, which was recrystallized from dichloromethane and methanol to give colorless crystals suitable for single-crystal X-ray diffraction. And the X-ray structure of **5a**. 2HCl was shown in Fig 3. The spectrum clearly indicates the existence of urea alcohol



Scheme-4: Cyclization of aldehyde **4** to form urea alcohol **5.**

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