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Supporting Information

Synthesis of bioactive evodiamine and rutaecarpine analogues under a ball milling condition

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Contents

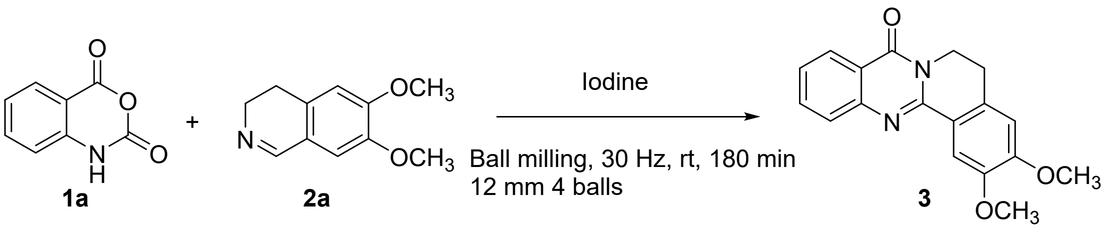
Experimental

Optimization of ball milling conditions for oxidation and its equivalent of 3

The **1a** (0.5 mmole), **2a** (1.3 equivalent), and difference equivalent of $KMnO_4$ or iodine were added in the ball milling jars (25 mL), and the condition of the same ball milling frequency, ball size and number, and reaction temperature and time were used in the same oxidation conditions.

Table S1. Optimization of ball milling conditions for oxidation and its equivalent.[a]

Entry	Equivalent of oxidation	Yield (%)
1	0.3	18
2	0.5	45
3	0.7	26
4	1.0	20



Entry	Equivalent of oxidation	Yield (%)
5	0.3	50

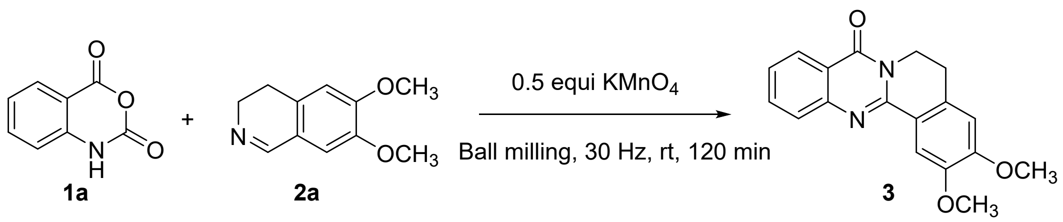
6	**0.4**	**59**
7	**0.5**	**61**
8	**0.7**	**26**

[a] The equivalent of 1a to 2a was 1 : 1.3. [b] Isolated yield.

Optimization of ball milling conditions for ball size and numbers of 3

The **1a** (0.5 mmole), **2a** (1.3 equivalent), and $KMnO_4$ (0.5 equivalent) were loaded into the stainless-steel jar and 5- or 12- mm milling balls were putted in the jar from one to eight and one to four balls, respectively. These conditions were reacted 120 min in ball milling at 30 Hz and room temperature. The maximum number of 12 mm milling balls is determined by the volume of jar, and 5mm milling ball is according to the trend of isolated yields. In the series conditions, three 5 mm balls displayed the best isolated yield, and the four 12 mm balls condition displayed the best yield in the 12 mm ball conditions.

Table S2. Optimization of ball milling conditions for ball size and numbers.[a]



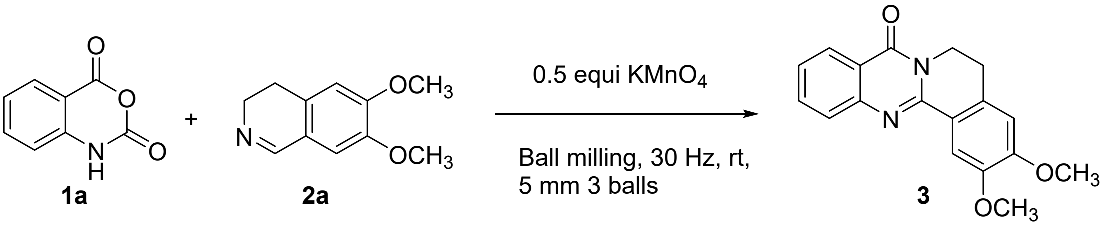
Entry	Ball size (mm)	Ball numbers	Yield (%)[b]
9	**5**	**1**	**26**
10	**5**	**2**	**30**
11	**5**	**3**	**54**
12	**5**	**4**	**51**
13	**5**	**5**	**26**
14	**5**	**6**	**30**
15	**5**	**7**	**34**
16	**5**	**8**	**17**
17	**12**	**1**	**36**
18	**12**	**2**	**28**
19	**12**	**3**	**44**
20	**12**	**4**	**45**

[a] The equivalent of 1a to 2a was 1 : 1.3. [b] Isolated yield.

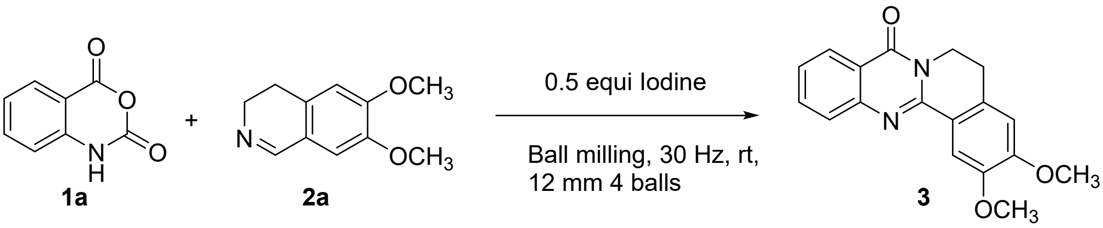
Optimization of ball milling conditions for time-dependent

The **1a** (0.5 mmole), **2a** (1.3 equivalent), and $KMnO_4$ (0.5 equivalent) or iodine (0.5 equivalent) were loaded into the stainless-steel jar and three 5- or four 12- mm milling balls were putted in the jar, respectively. These conditions were reacted from 60 min in ball milling at 30 Hz and room temperature. The maximum reaction time dependents on the trend of yield. In the series conditions, $KMnO_4$ conditions displayed the best isolated yield at 120 min, and iodine condition displayed the best isolated yield in 180 min.

Table S3. Optimization of ball milling conditions for time-dependent.[a]



Entry	Time (min)	Yield (%)
21	60	29
22	90	44
23	120	54
24	150	28
25	180	22



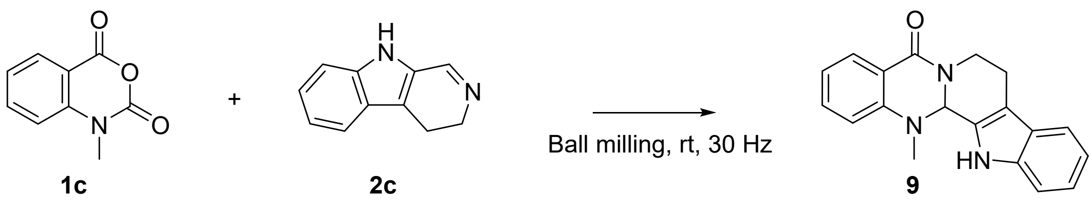
Entry	Time (min)	Yield (%)
26	60	30
27	90	41
28	120	56
29	150	59
30	180	61
31	210	45

[a] **The equivalent of 1a to 2a was 1 : 1.3.** [b] **Isolated yield.**

Optimization of ball milling conditions for time-dependent for evodiamine

The **1c** (0.5 mmole), **2c** (1 or 1.3 equivalent) were subjected into the stainless-steel jar with three 5- or four 12- mm milling balls. These conditions were reacted in ball milling at 30 Hz and room temperature. The maximum reaction time dependents on the TLC results. Between the entries 32 and 33, the equivalents of **1c** and **2c** are not affect the yield. Furthermore, the yield of 5-mm balls condition display 20% benefit more than 12-mm balls condition.

Table S4. Optimization of ball milling conditions for evodiamine.



Entry	Equivalent of 1c to 2c	Ball size (mm)	Ball numbers	Time	Yield (%)
32	1 : 1.3	12	4	45	48
33	1 : 1	12	4	45	51
34	1 : 1	5	3	90	63

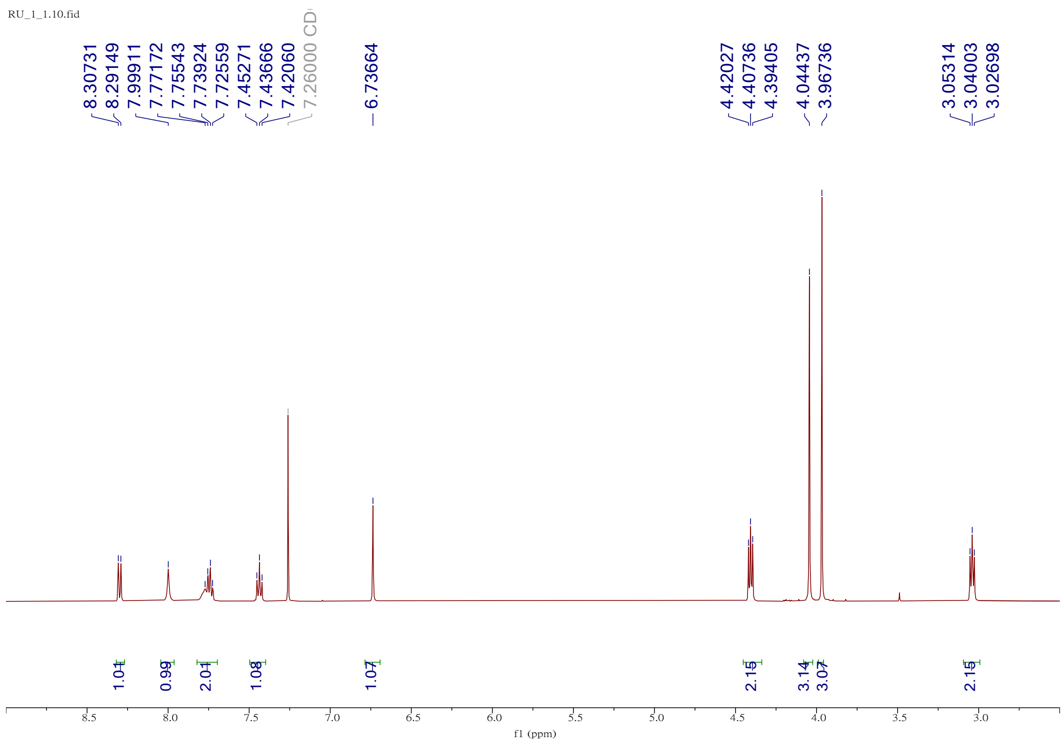


Fig S1. ^{1}H NMR spectrum of 2,3-dimethoxy-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (3)

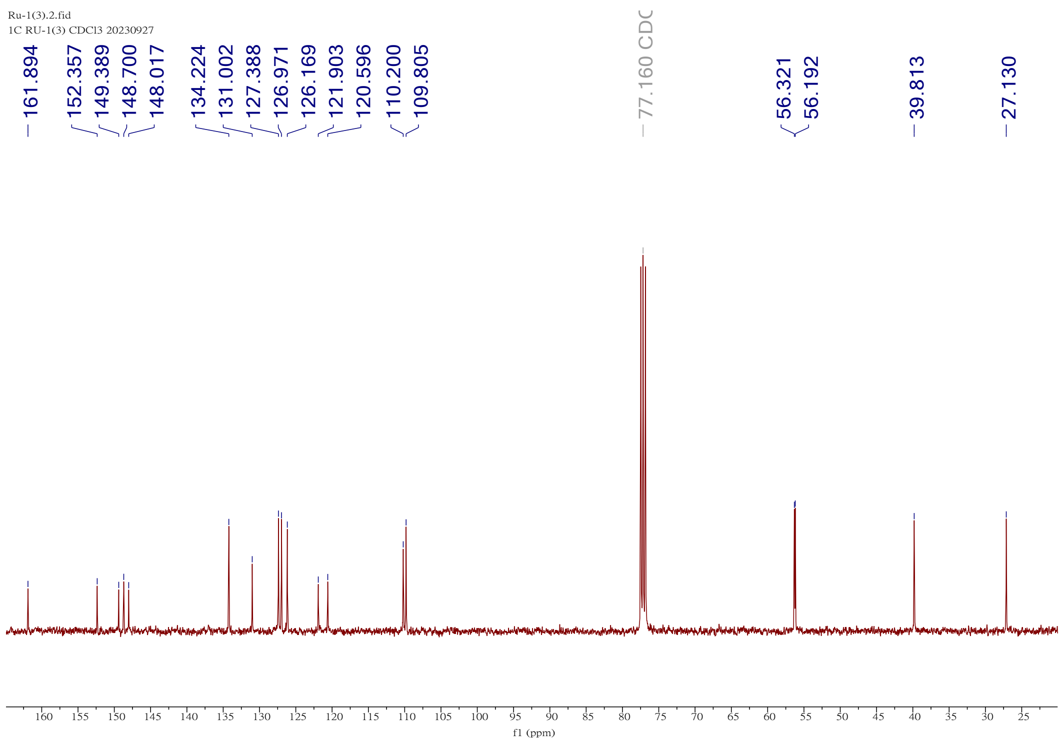


Fig S2. ^{13}C NMR spectrum of 2,3-dimethoxy-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (3)

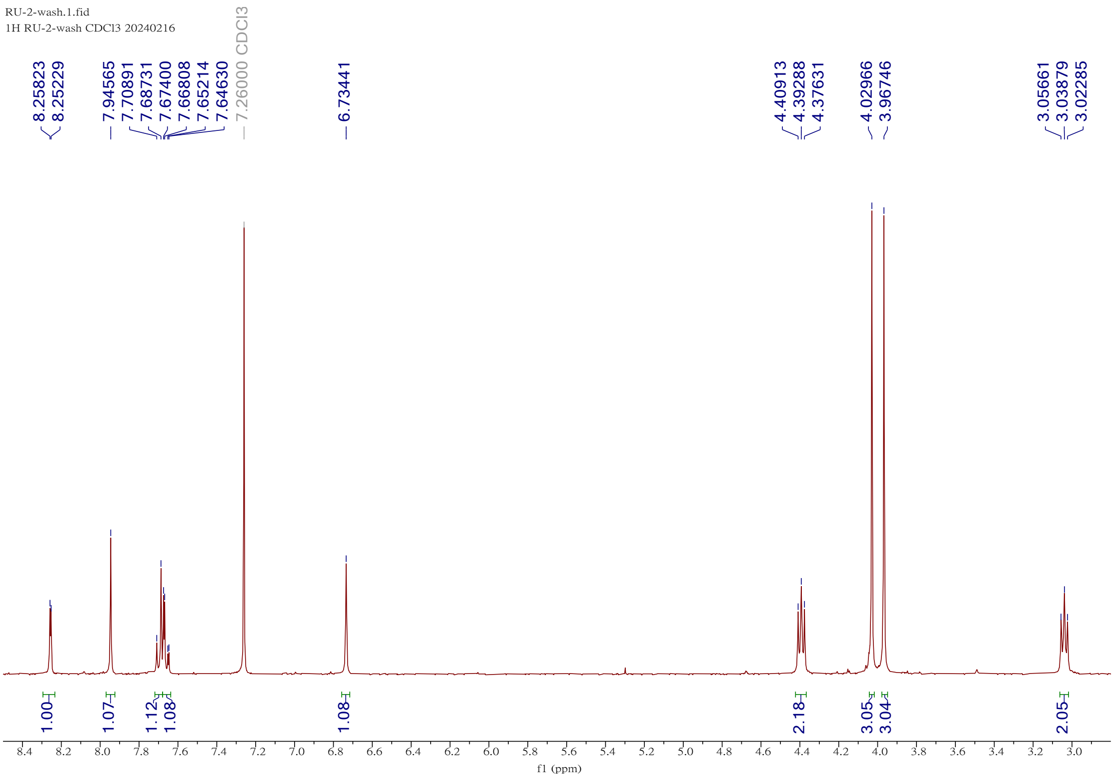


Fig S3. ^{1}H NMR spectrum of 10-chloro-2,3-dimethoxy-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (4)

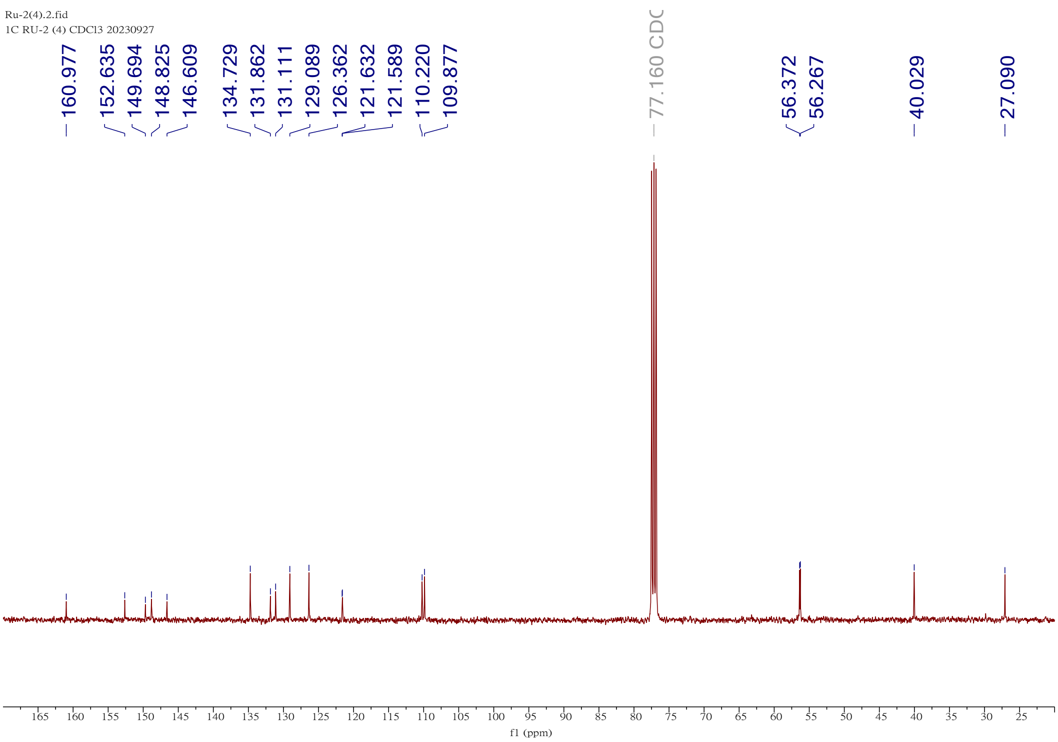


Fig S4. ^{13}C NMR spectrum of 10-chloro-2,3-dimethoxy-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (4)

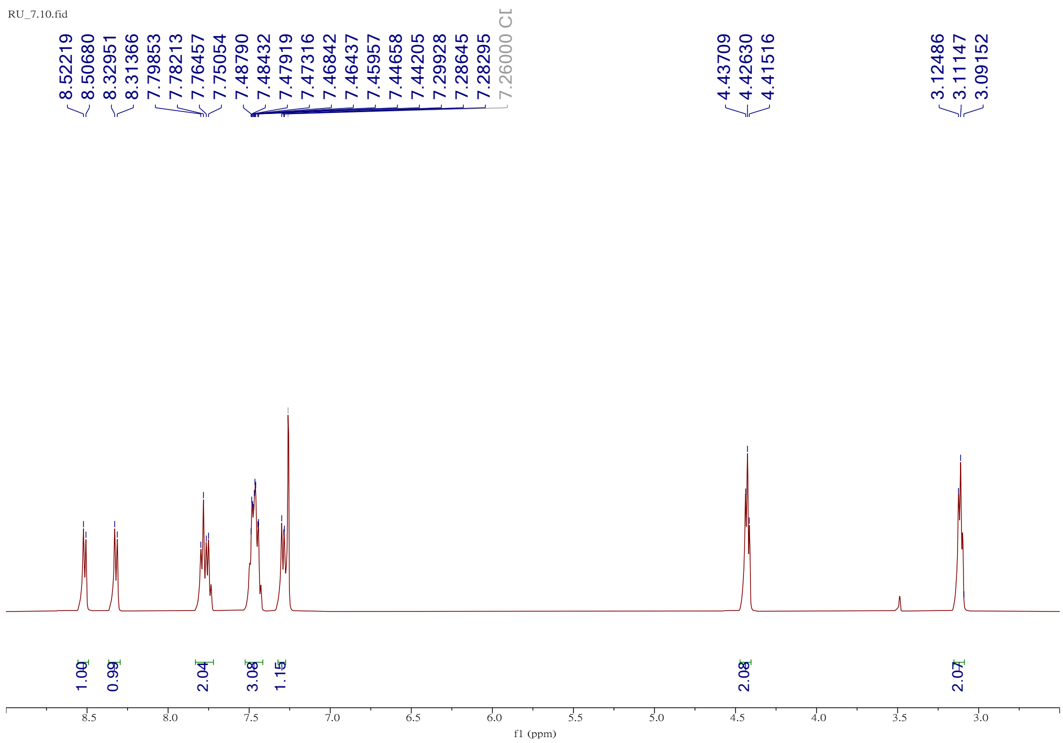


Fig S5. [1]H NMR spectrum of 5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (5)

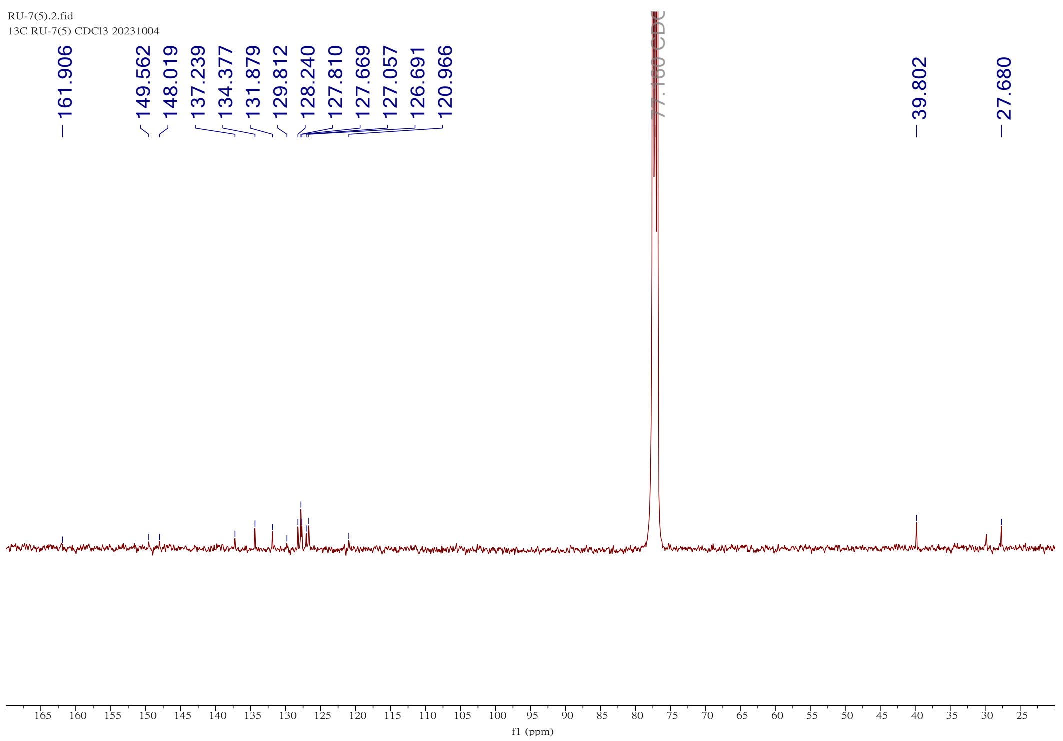


Fig S6. [13]C NMR spectrum of 5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (5)

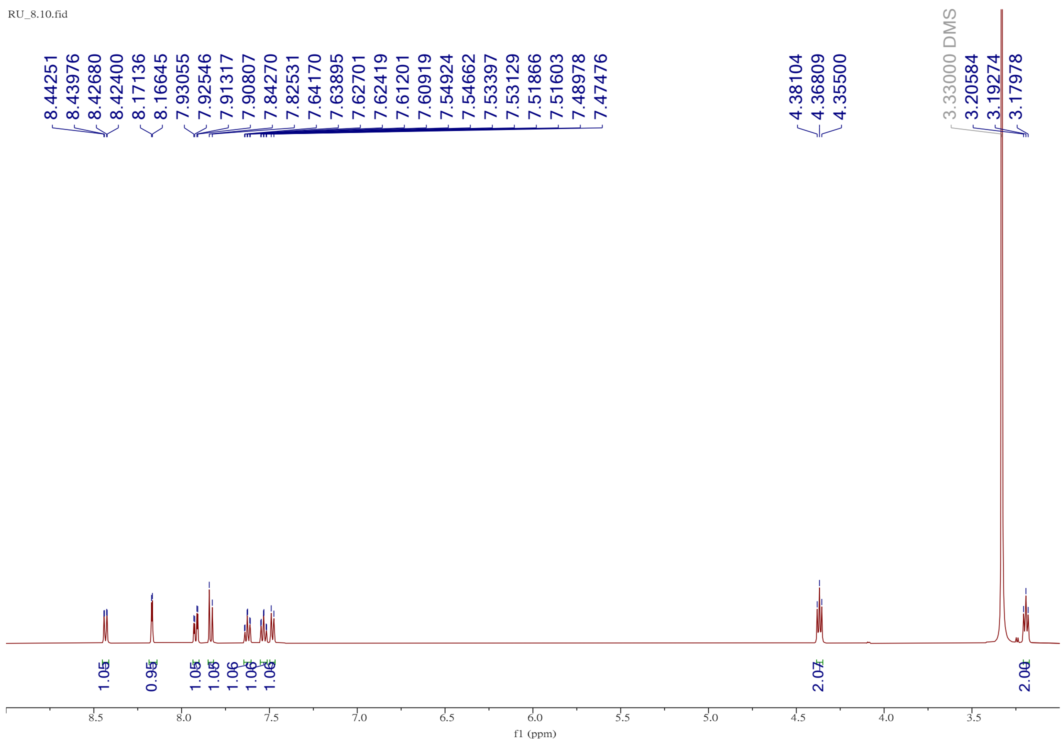


Fig S7. ^{1}H NMR spectrum of 10-chloro-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (6)

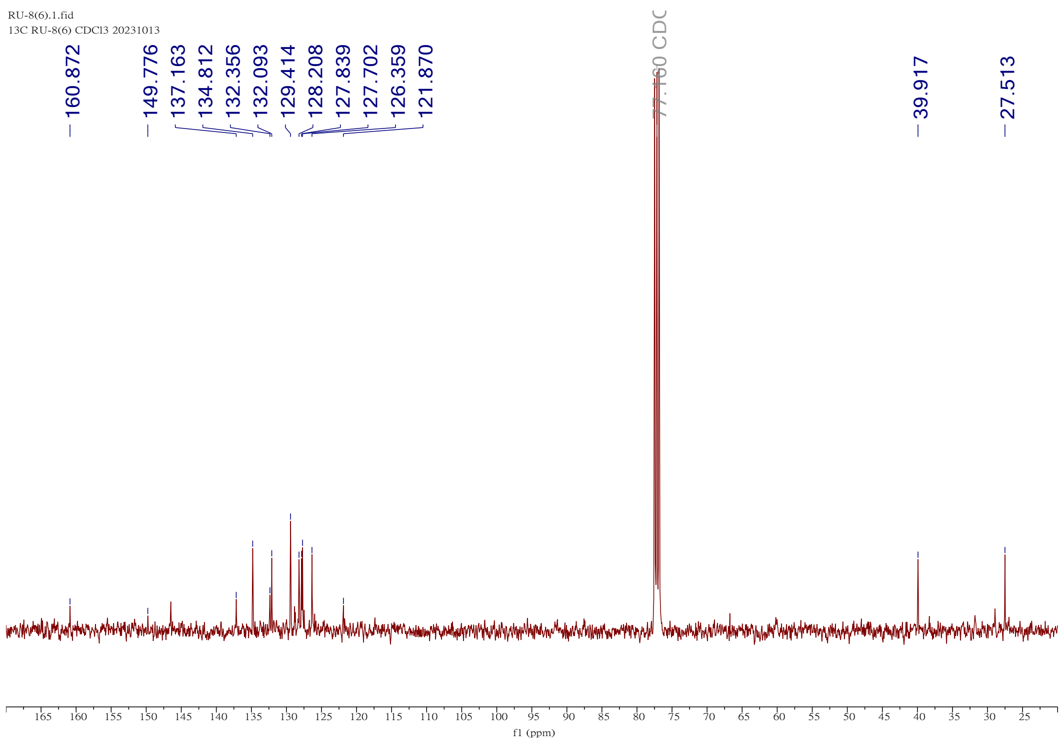


Fig S8. ^{13}C NMR spectrum of 10-chloro-5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one (6)

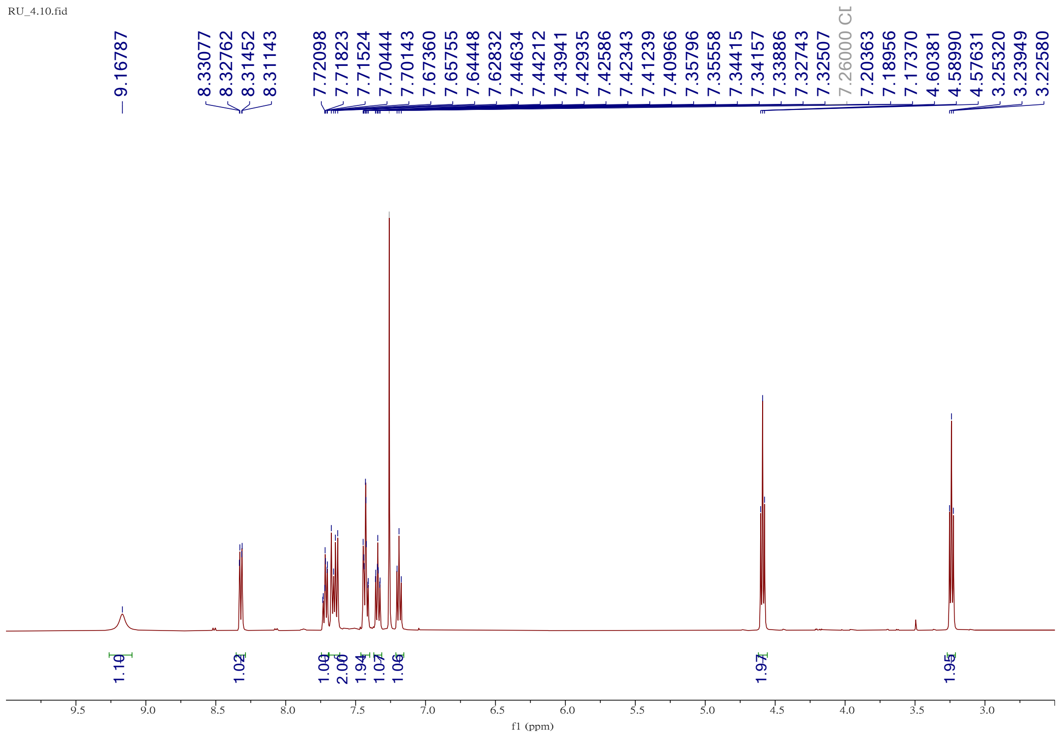


Fig S9. ^{1}H NMR spectrum of rutaecarpine (7)

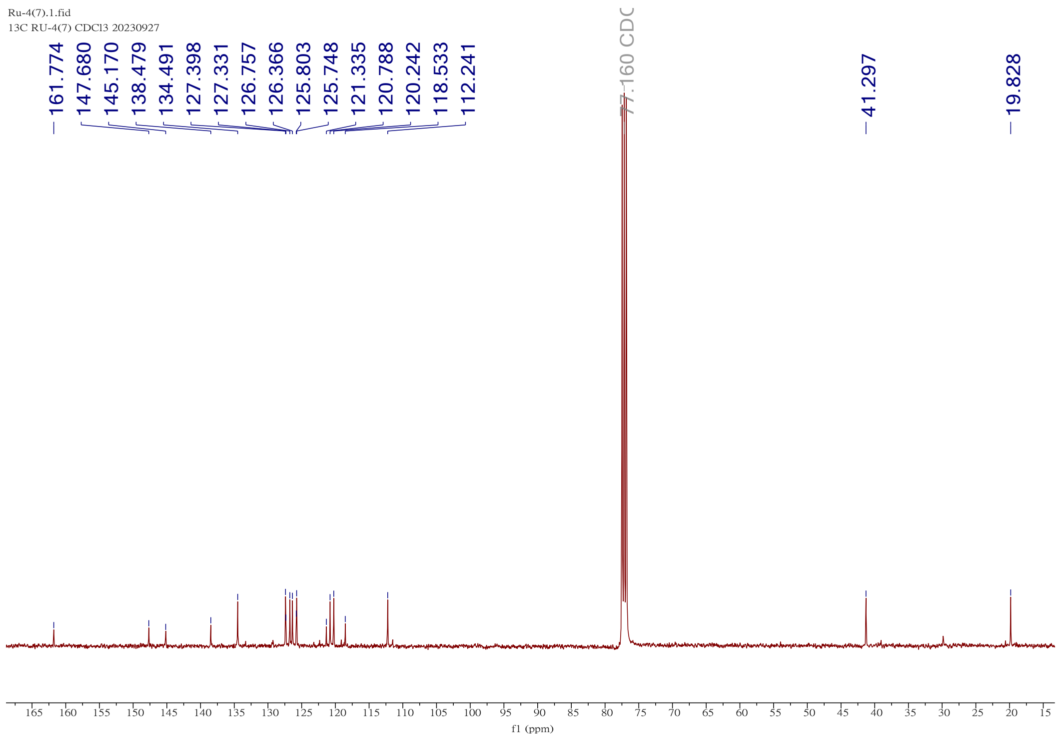
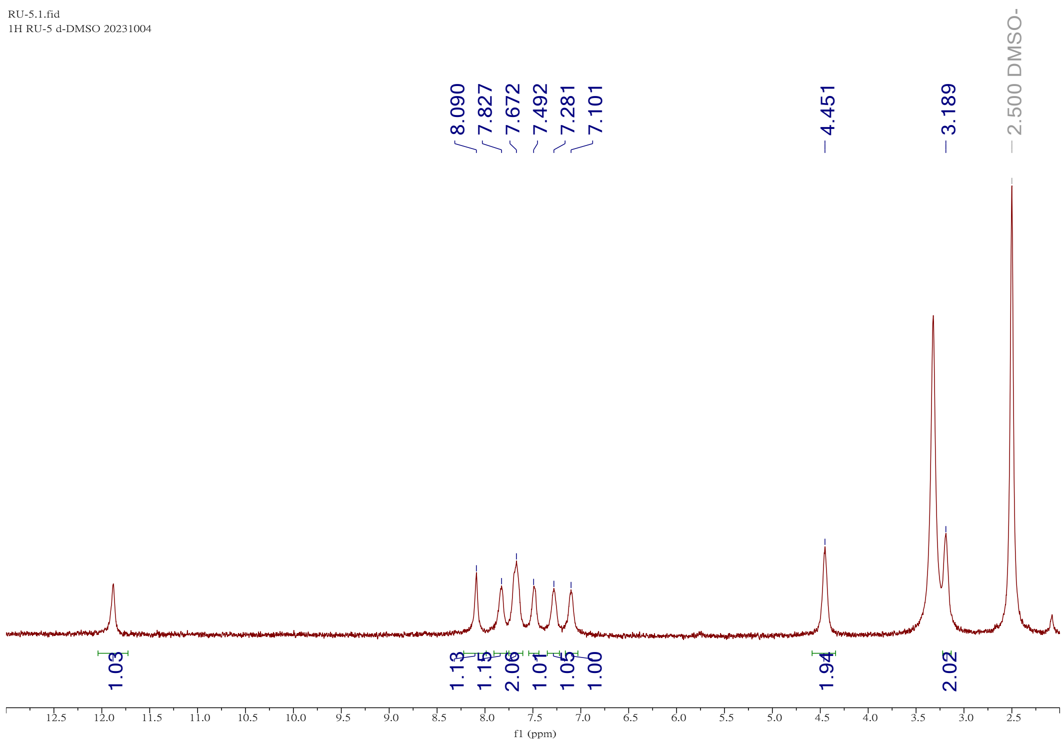


Fig S10. ^{13}C NMR spectrum of rutaecarpine (7)



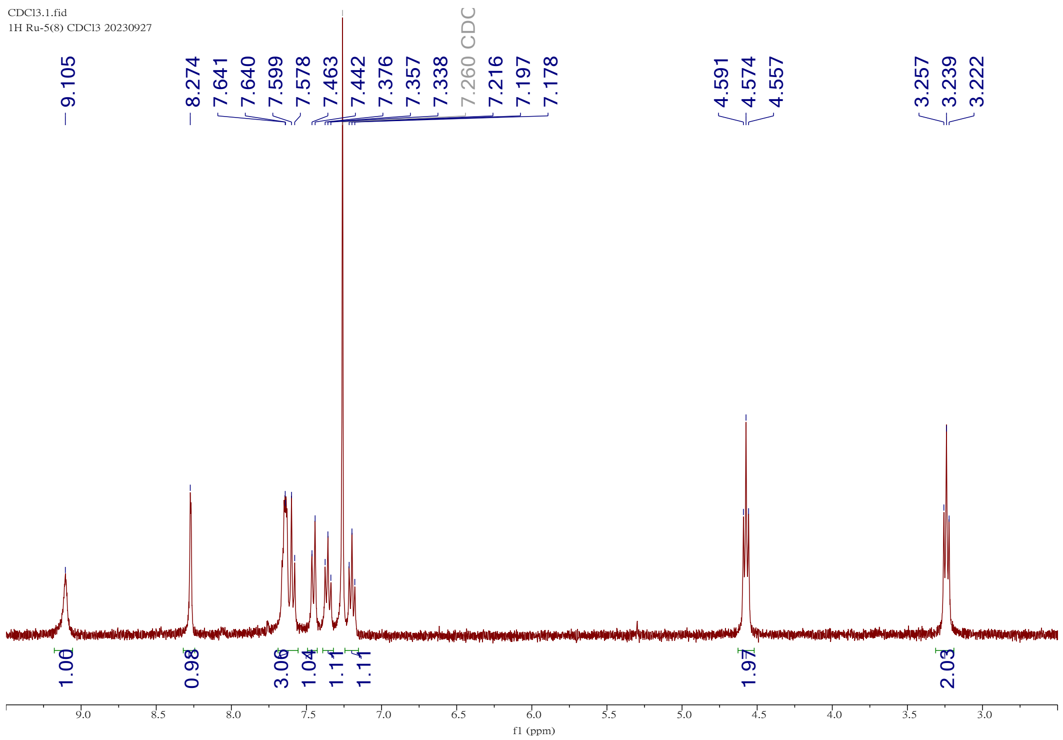
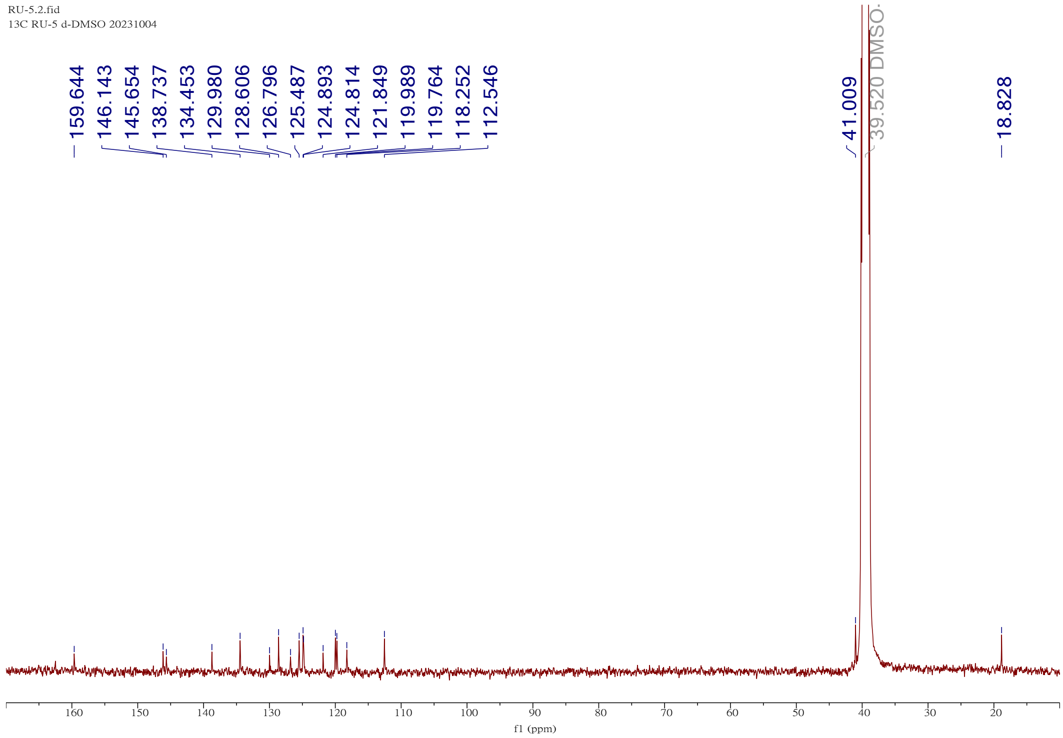


Fig S11. ^{1}H NMR spectrum of 3-chlororutaecarpine (8)



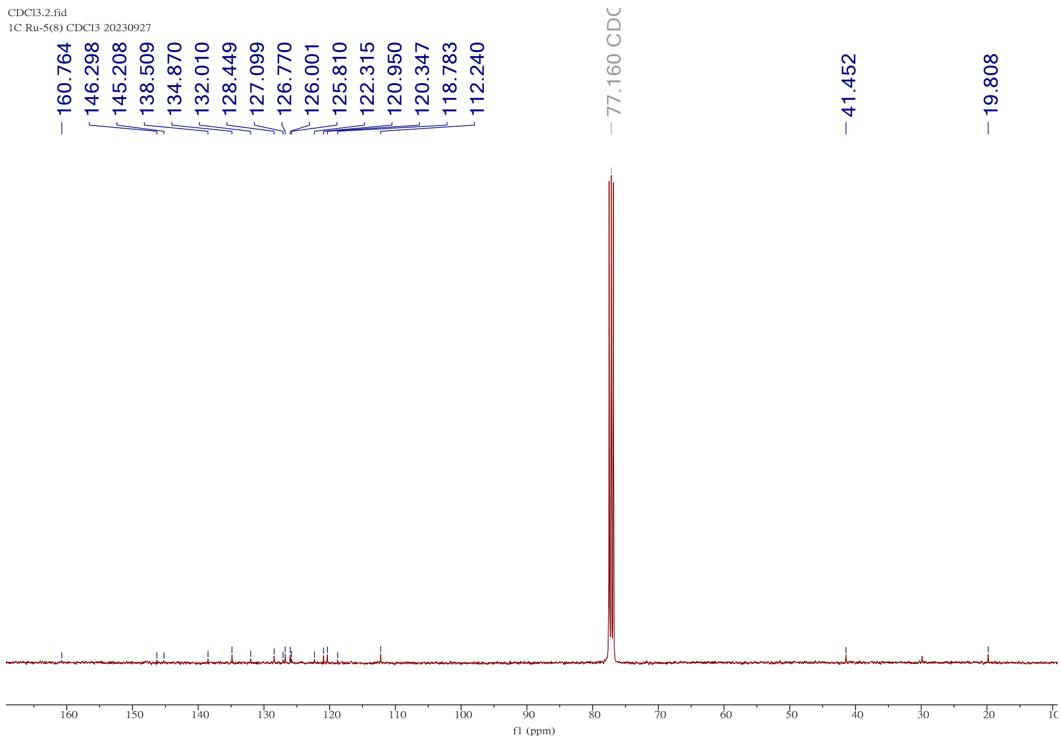


Fig S12. ^{13}C NMR spectrum of 3-chlororutaecarpine (8)

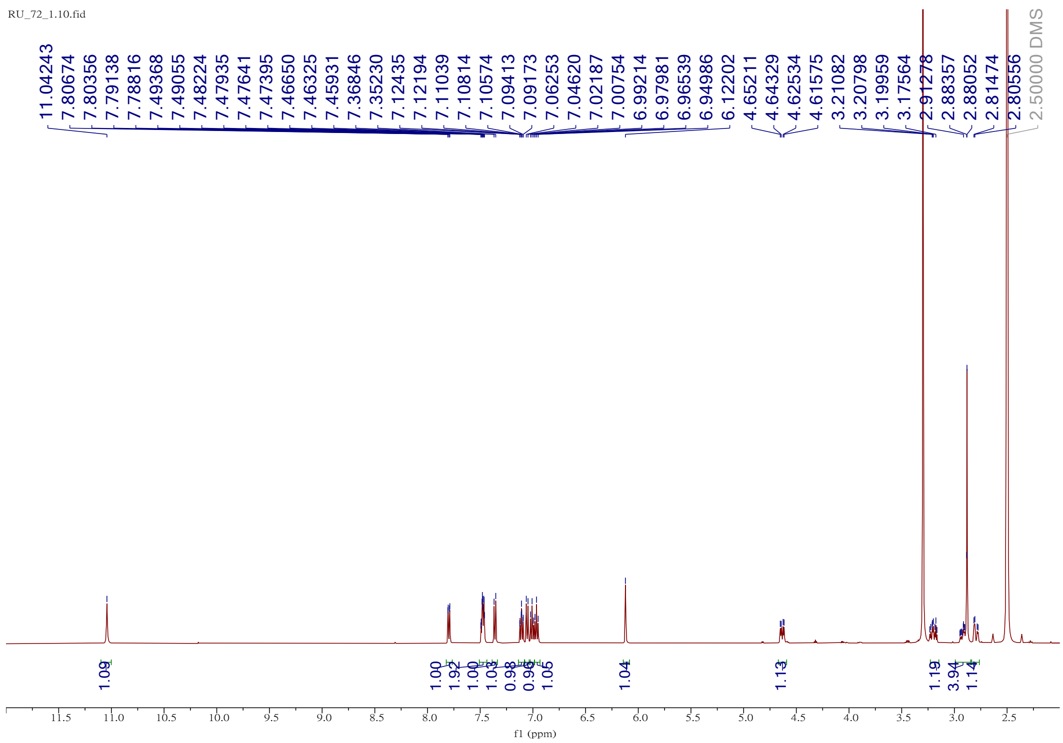


Fig S13. ¹H NMR spectrum of (±)-evodiamine (9)

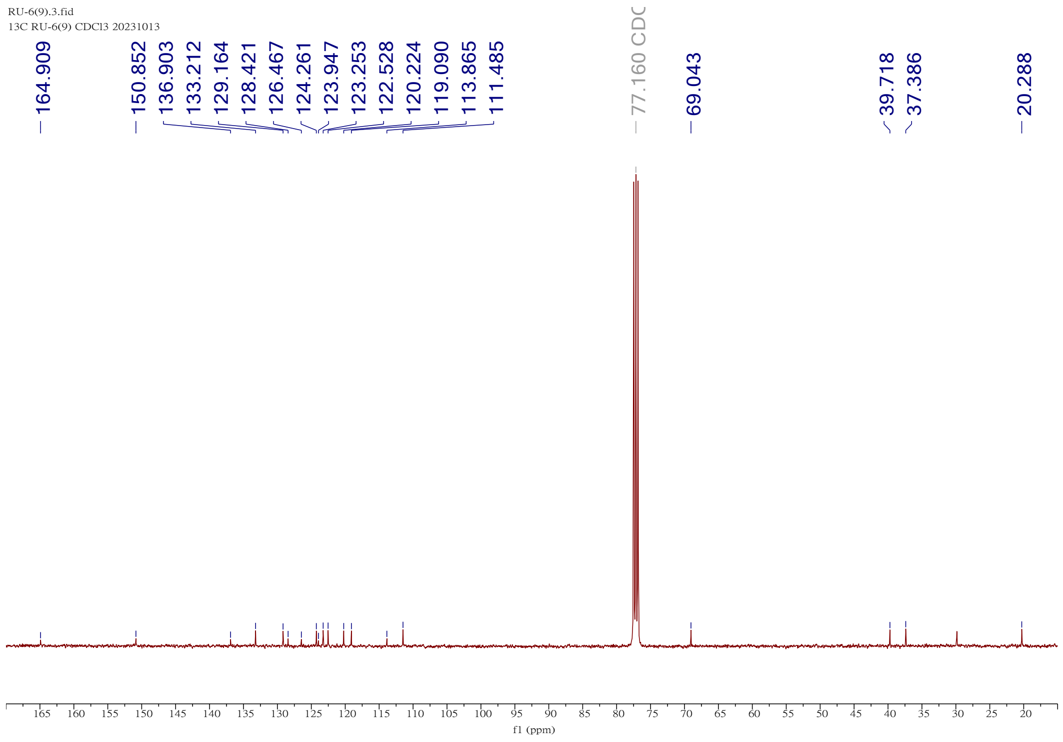


Fig S14. ¹³C NMR spectrum of (±)-evodiamine (9)

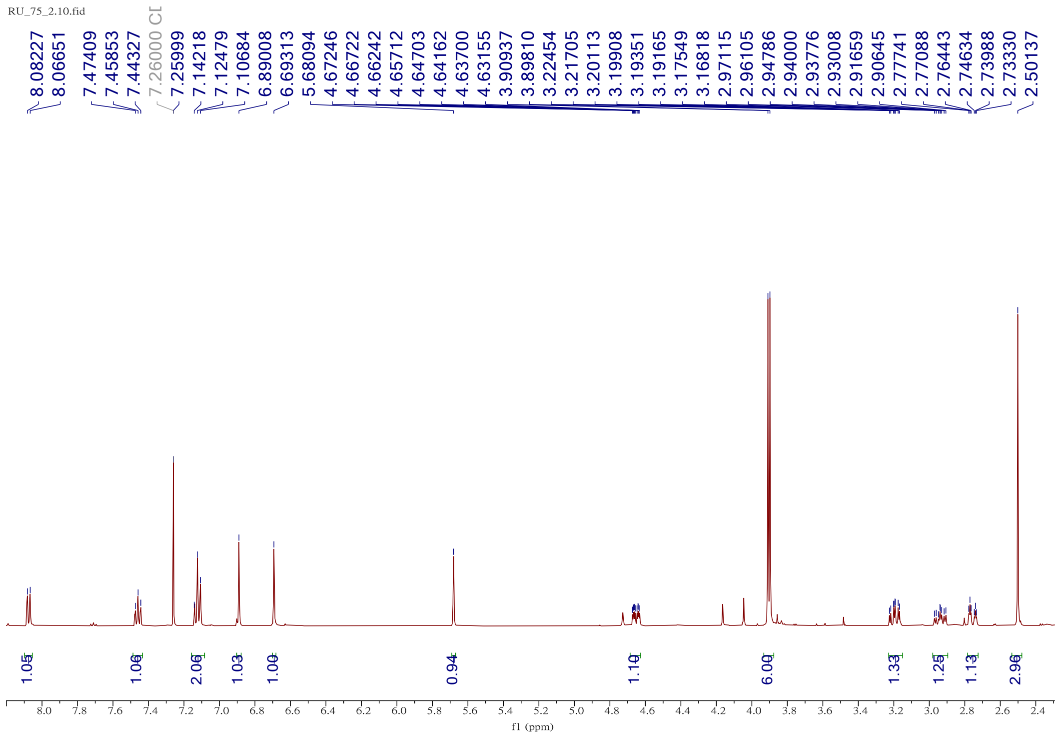


Fig S15. [1]H NMR spectrum of 2,3-dimethoxy-13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b] quinazolin-8-one (10)

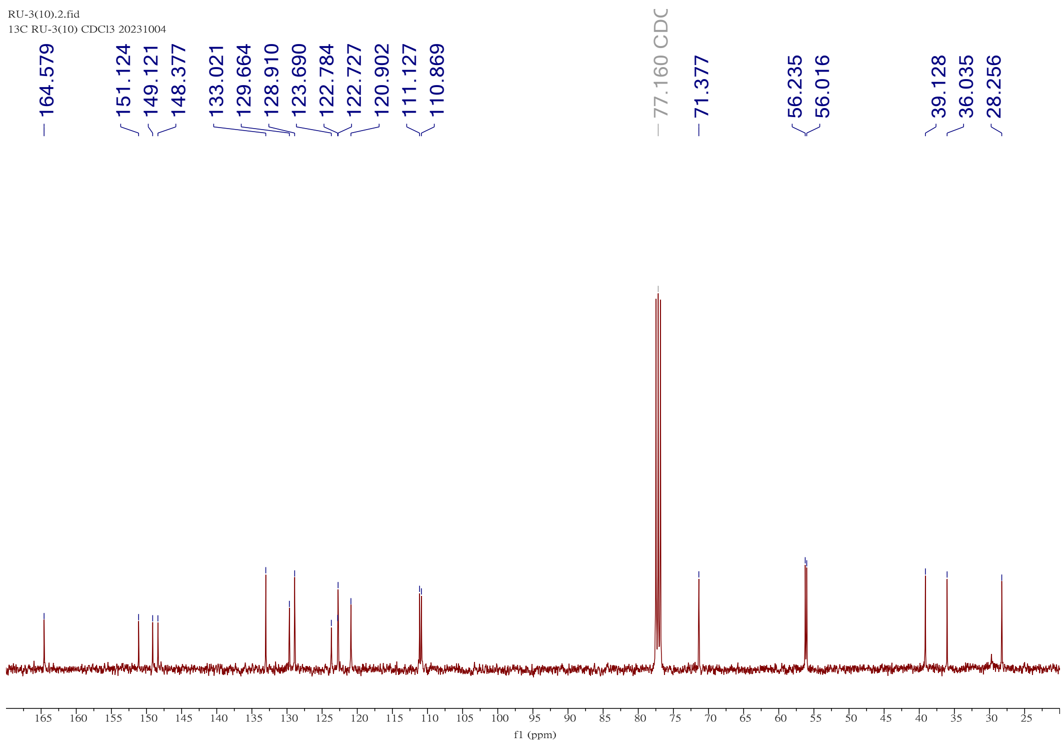


Fig S16. [13]C NMR spectrum of 2,3-dimethoxy-13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b] quinazolin-8-one (10)

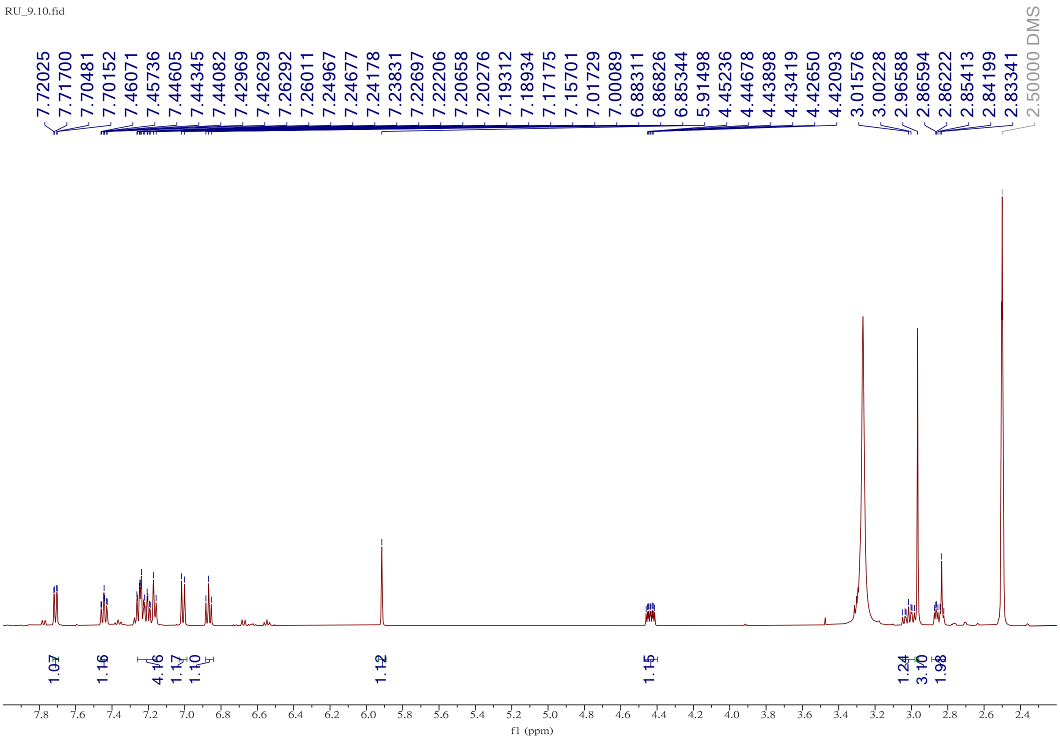


Fig S17. ^{1}H NMR spectrum of 13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b]quinazolin-8-one (11)

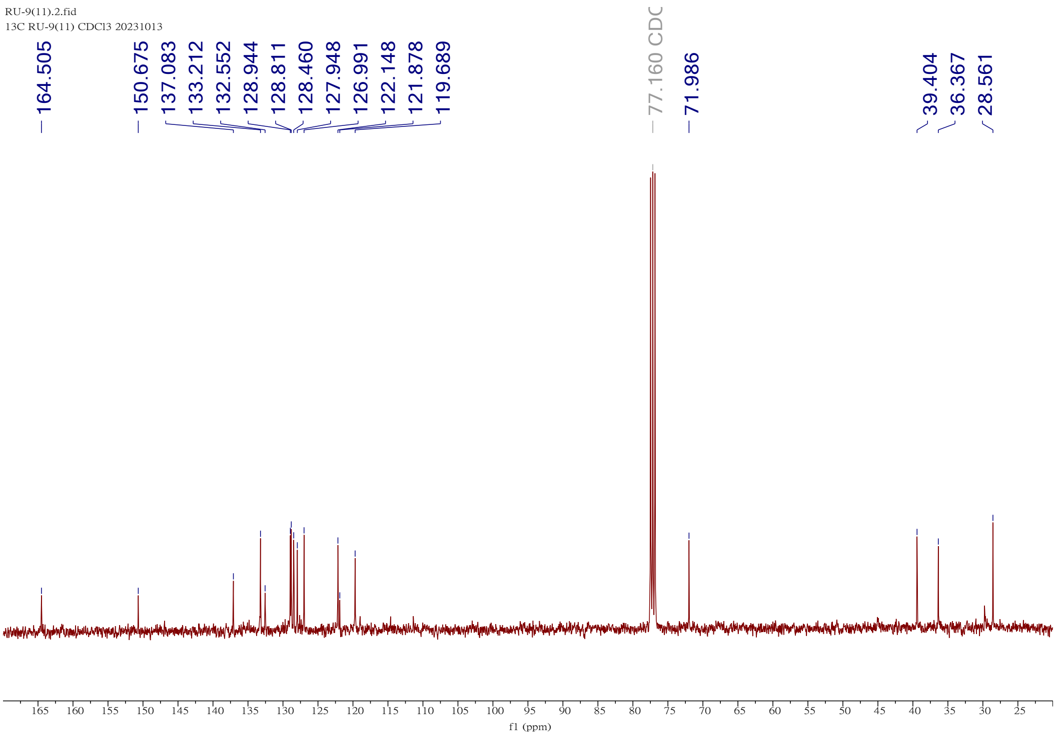


Fig S18. ^{13}C NMR spectrum of 13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b]quinazolin-8-one (11)