Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Two Approaches for the Synthesis of Levo-Praziquantel

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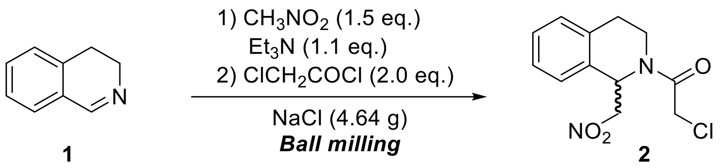
1. Mechanochemical Parameters Screening of Aza-Henry Reaction

Table S1. Screening of Mechanochemical Parameters of Aza-Henry Reaction[a]



entry	v_{rot}	Φ_{MB}	time (min)	yield (%)[b]
1	100	0.13	30+10	72
2	150	0.13	30+10	75
3	**200**	**0.13**	**30+10**	**83**
4	250	0.13	30+10	77
5	300	0.13	30+10	76
6	200	0.05	30+10	54
7	200	0.09	30+10	79
8	200	0.17	30+10	65
9	200	0.13	10+10	78
10	200	0.13	50+10	82
11	200	0.13	70+10	81
12	200	0.13	30+2	74
13	200	0.13	30+6	80
14	200	0.13	30+14	81
15	200	0.13	30+18	80

[a] Reaction conditions: **1** (1 mmol), nitromethane (1.5 mmol), Et_3N (1.1 mmol), and NaCl (4.64 g) were placed in a 50 mL stainless steel vessel with stainless-steel ball (d_{MB} = 6 mm) on a planetary mill, milling at a certain rotation speed for certain minutes, then chloracetyl chloride was added and milling for certain minutes. [b] Yield of **2** based on **1**.

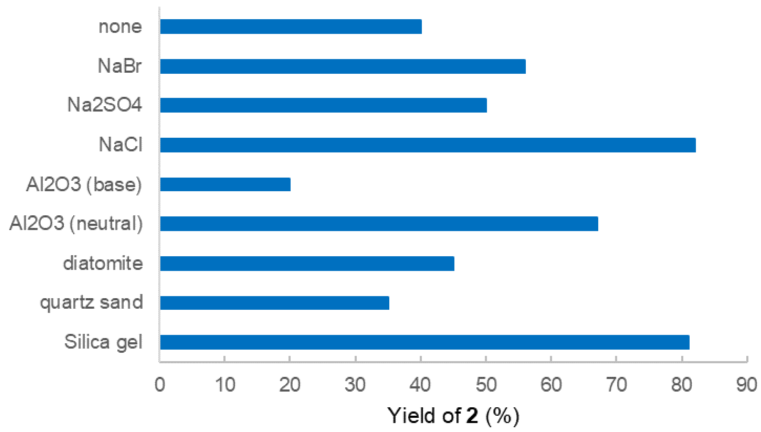
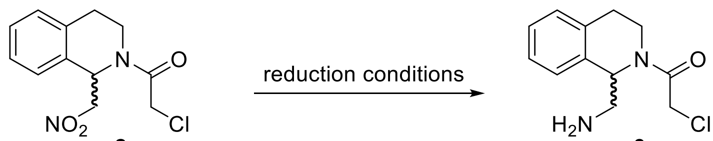


Figure S1. Screening of the Grinding Auxiliary of Aza-Henry Reaction[a]

[a] **1** (1 mmol), nitromethane (1.5 mmol), Et_3N (1.1 mmol) and grinding auxiliary (V_{ga} = 2.15 cm^3) were placed in a 50 mL stainless steel vessel with stainless-steel ball on a planetary mill, milling at 200 rpm for 30 min, then chloracetyl chloride was added and milling for 10 min. Yield of **2** based on **1**.

2. Reaction Conditions Optimization of Reduction Reaction

Table S2. Screening of Reduction Reaction Condition



entry	conditions	yield (%)[a]
1	Raney Ni (0.5 mL), $NH_3{\cdot}H_2O$ (1.0 mL), H_2 (1 atm), MeOH (10 mL), r.t., 4 h	74
2[1]	$(NH_4)_2S$ (10 eq.), THF (10 mL), r.t., 4 h	trace
3[2]	Pd/C (10% Pd basis, 0.15 mmol), H_2 (1 atm), EtOAc/MeOH = 2:1 (10 mL), reflux, 6 h	trace
4[2]	iron powder (5 eq.), NH_4Cl (10 eq.), $MeOH/H_2O$ = 1:1 (10 mL), reflux, 4 h	80

[a] Yield of **3** based on **2** (1 mmol).

Table S3. Screening of Raney Ni Catalyzed Reduction Condition[a]

entry	solvent/additive (mL)	temperature (°C)	time (h)	yield (%)[b]
1	EtOH/NH_3·H_2O = 10/1 (11)	r.t.	4	47
2	THF/NH_3·H_2O = 10/1 (11)	r.t.	4	44
3	$PhCH_3$/NH_3·H_2O = 10/1 (11)	r.t.	4	58
4	MeOH/NH_3·H_2O = 10/1 (11)	r.t.	4	74
5	MeOH/NH_3·H_2O = 10/1 (11)	40	4	62
6	MeOH/NH_3·H_2O= 10/1 (11)	50	4	43
7	**MeOH/NH_3·H_2O = 10/1 (11)**	**r.t.**	**3**	**75**
8	MeOH/NH_3·H_2O = 10/1 (8)	r.t.	3	70
9	MeOH/NH_3·H_2O = 10/1 (15)	r.t.	3	73

[a] Reaction conditions: **2** (1 mmol), Raney Ni (0.5 mL, 100 g solid/125 mL water) were placed in a 25 mL two-necked flask with solution, stirring under an atmosphere of H_2 (15 psi) for certain hours. [b] Yield of **3** based on **2**.

3. Recovery and Reuse of the Resolution Agent

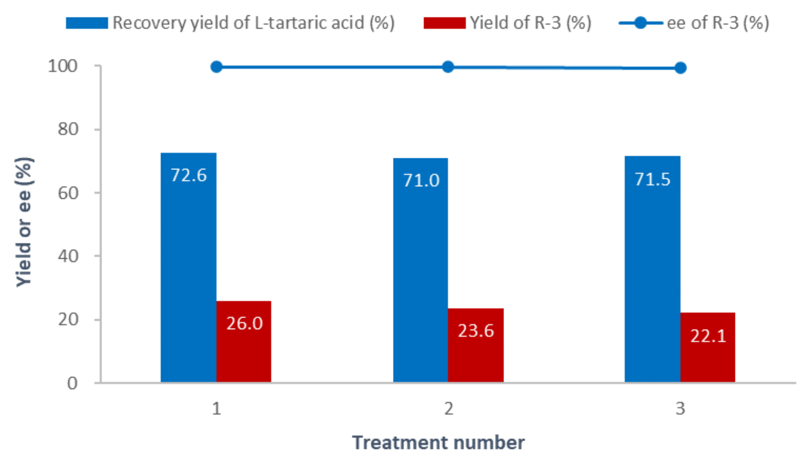
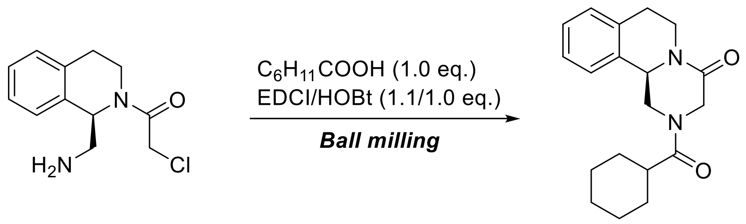


Figure S1. Recovery and Reuse of *L*-tartaric acid [a]

[a] Reaction conditions were consistent to those in Table 2, *L*-tartaric acid (0.5 eq) was used in each reaction.

4 Mechanochemical Parameters Screening of Acylation/Ring Closing Reaction

Table S4. Screening of Mechanochemical Parameters of Acylation/Ring Closing Reaction[a]



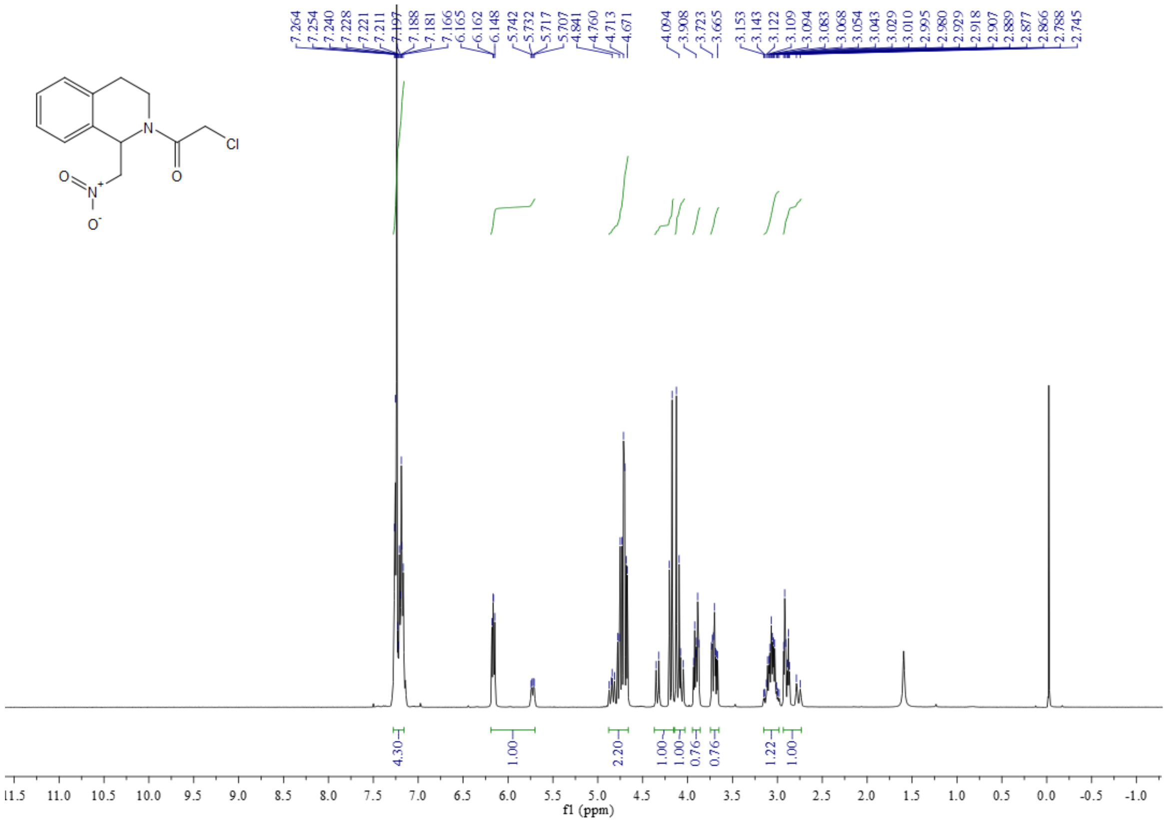
R-**3** *R*-PZQ

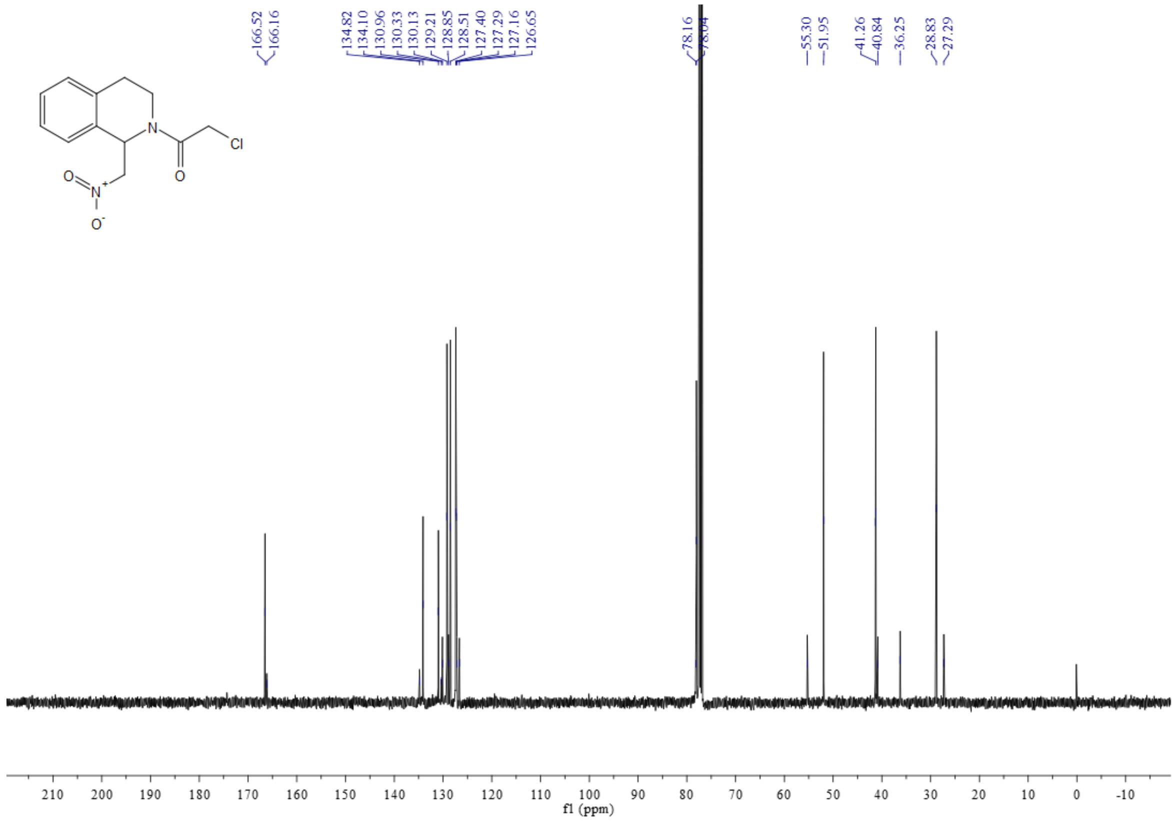
entry	v_{rot}	Φ_{MB}	time (min)	yield (%)[b]	*ee* (%)[c]
1	100	0.13	30+30	73	99.0
2	**200**	**0.13**	**30+30**	**84**	**99.7**
3	300	0.13	30+30	**77**	99.6
4	400	0.13	30+30	71	98.4
5	200	0.05	30+30	53	99.1
6	200	0.09	30+30	64	99.2
7	200	0.17	30+30	72	98.7
8	200	0.13	10+30	78	99.2
9	200	0.13	50+30	74	99.4
10	200	0.13	70+30	74	99.2
11	200	0.13	30+10	75	99.0
12	200	0.13	30+50	83	99.3
13	200	0.13	30+70	79	98.5

[a] Reaction conditions: cyclohexanecarboxylic acid (1.0 mmol), EDCI (1.0 mmol) and HOBt (1.0 mmol) were placed in a 50 mL stainless steel vessel with stainless-steel ball (dMB = 6 mm), milling at a certain rotation speed for certain minutes, then *R*-**3** (1.0 mmol) was added and milling for certain minutes. [b] Yield of *R*-PZQ based on *R*-**3**. [c] Determined by HPLC analysis.

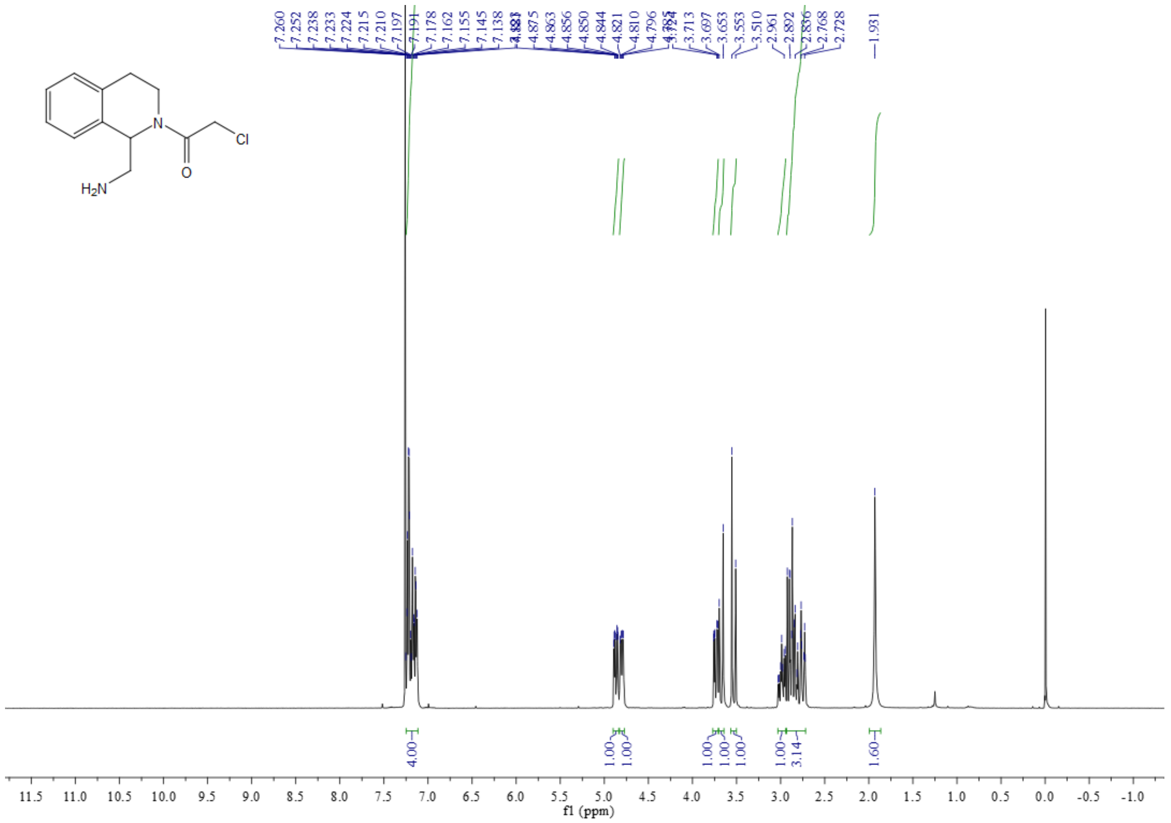
5. NMR Spectra

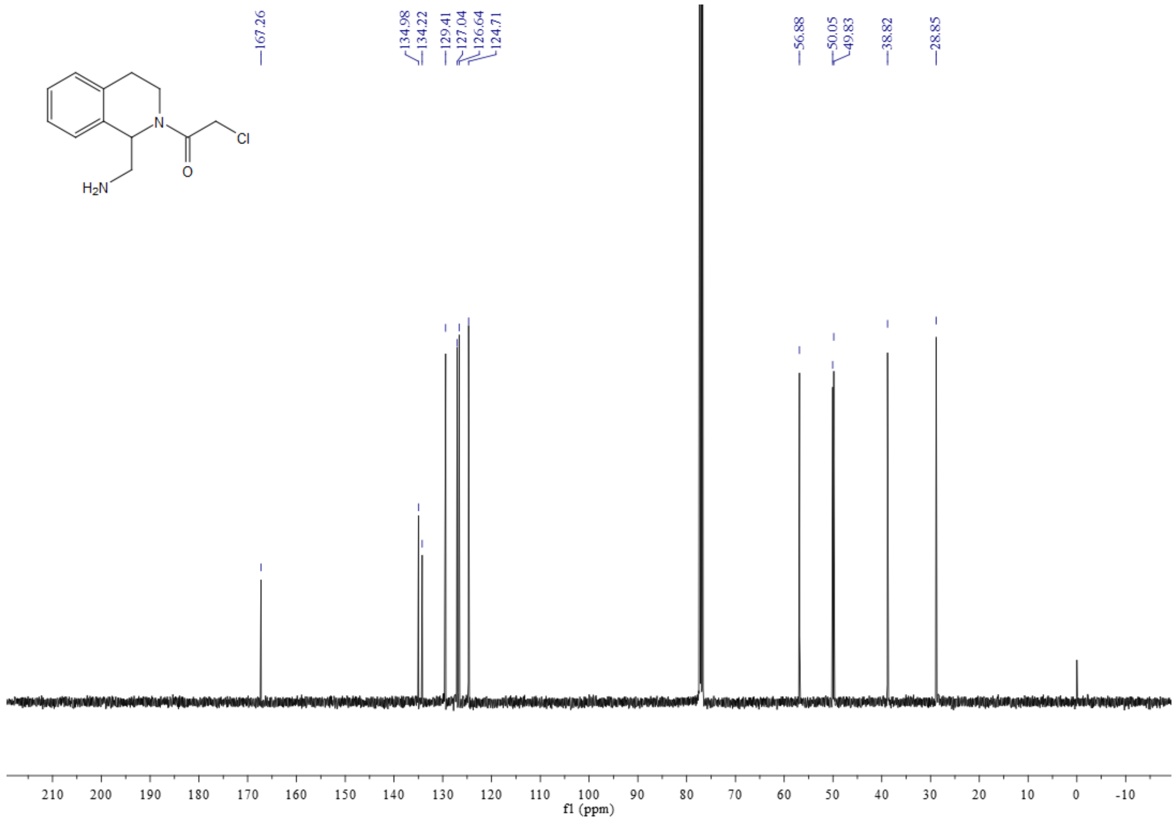
2-chloro-1-(1-(nitromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (**2**)



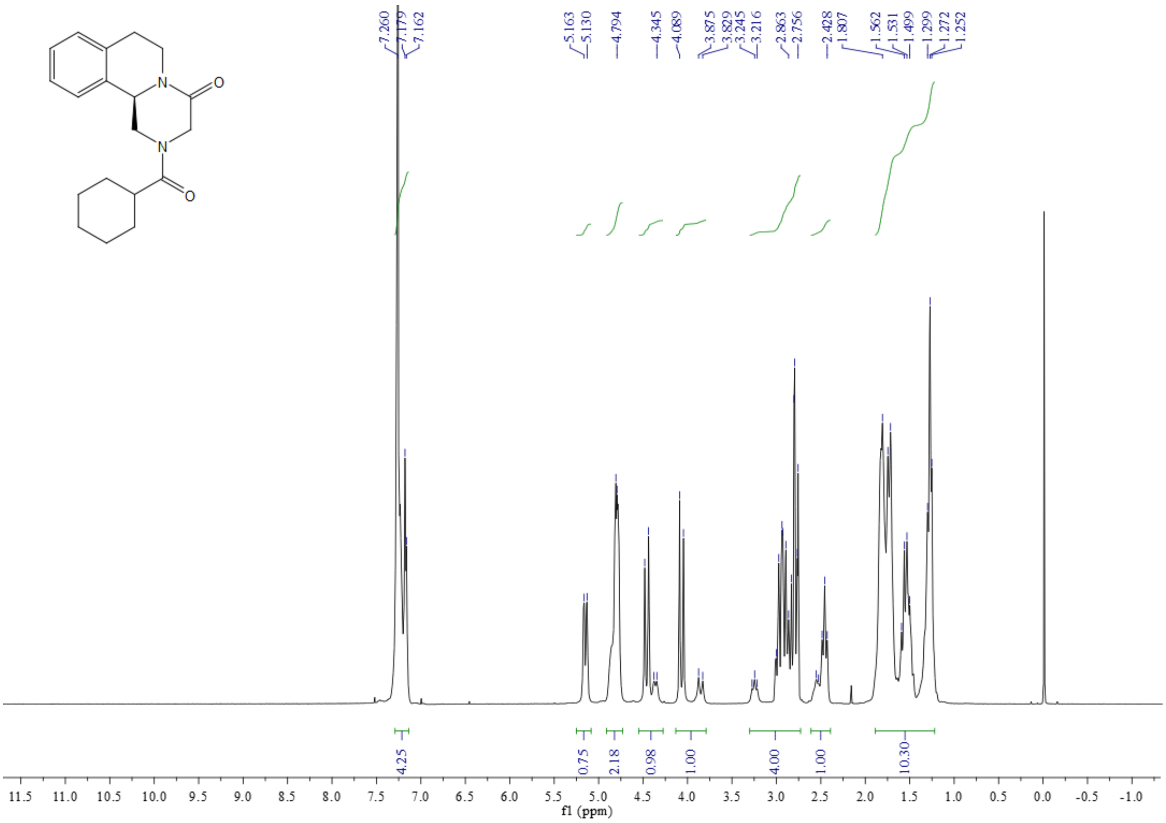


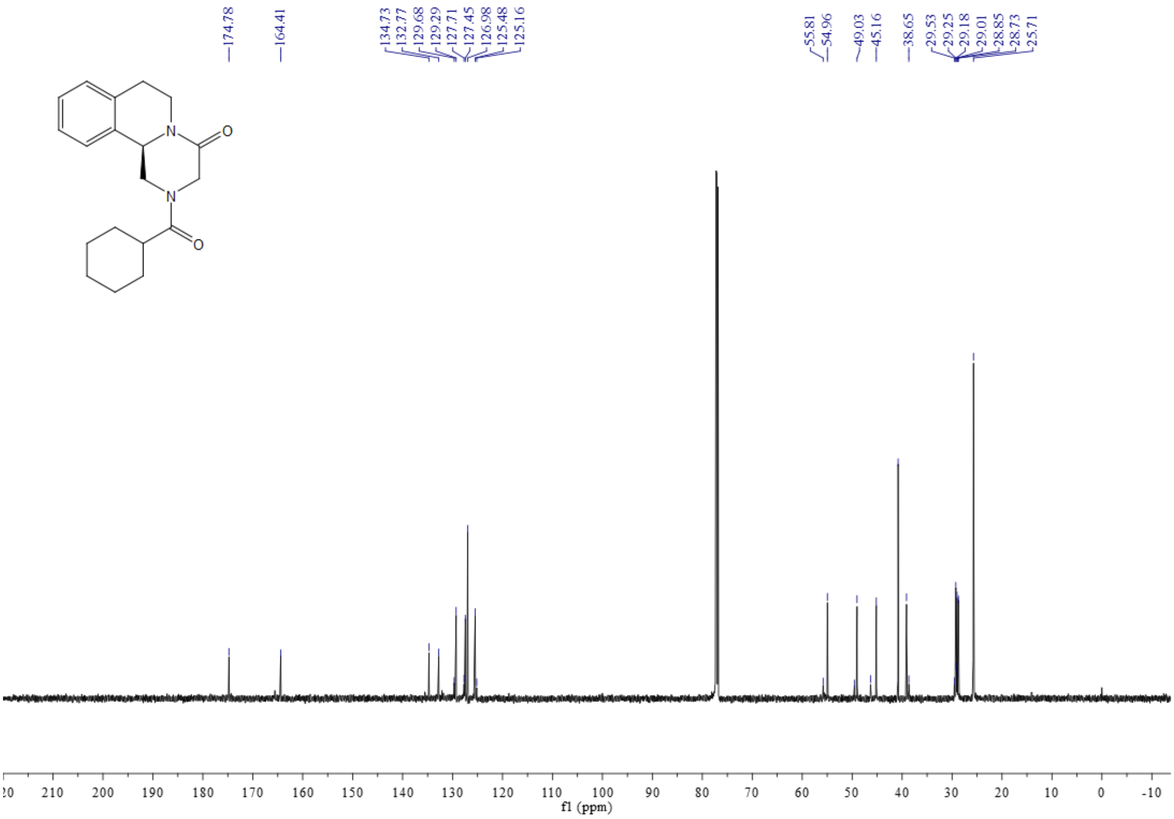
1-(1-(aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-chloroethan-1-one (**3**)





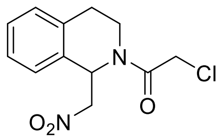
(R)-2-(cyclohexanecarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one
(***R*-PZQ**)



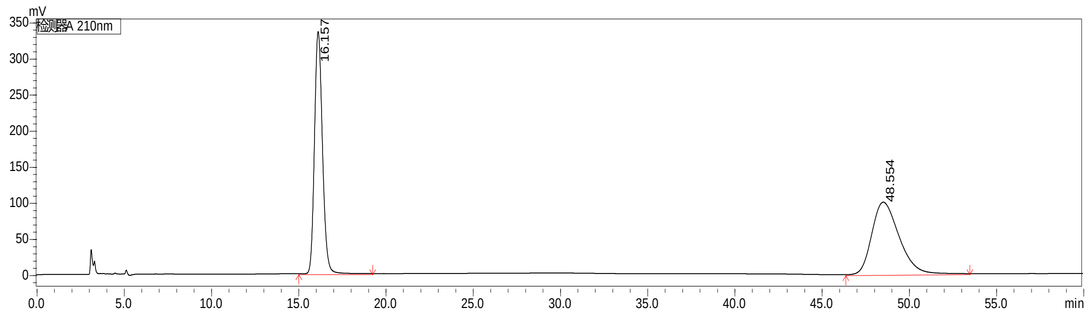


5. HPLC Spectra

2-chloro-1-(1-(nitromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (**2**)

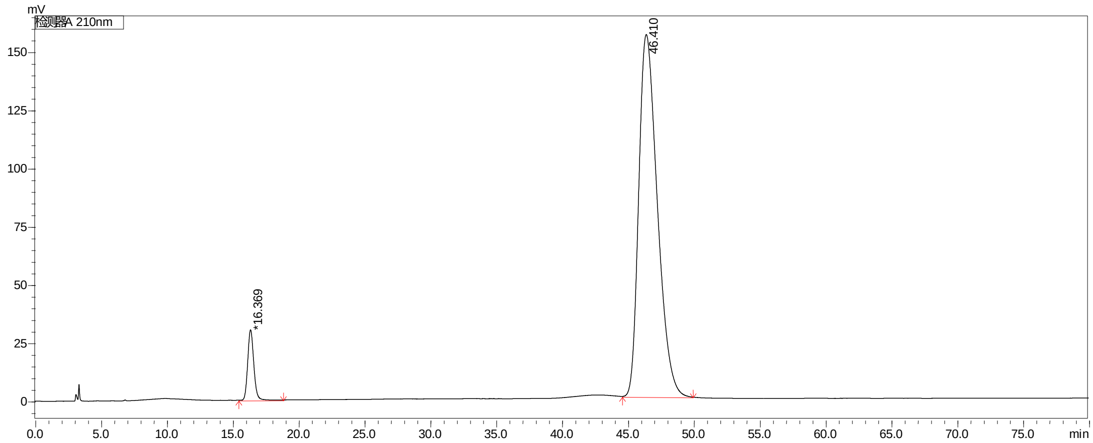


Racemic **2**



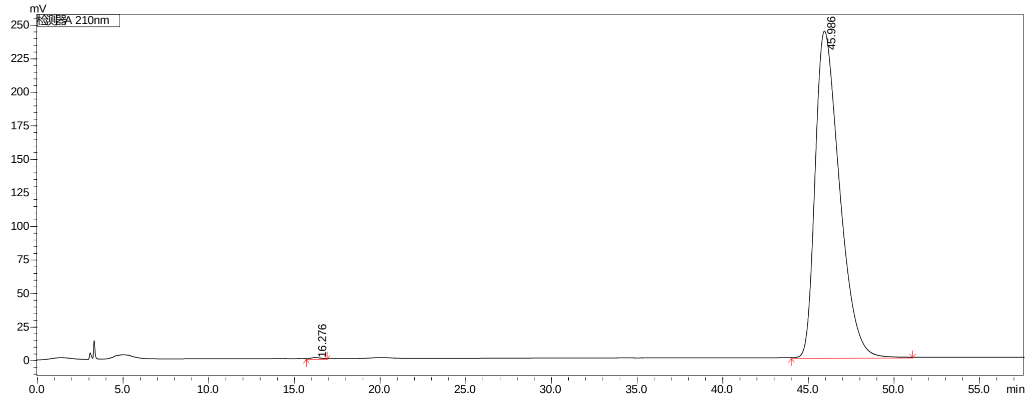
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	16.157	10640369	335823	49.627	49.627
2	48.554	10800487	99985	50.373	50.373

R-**2**



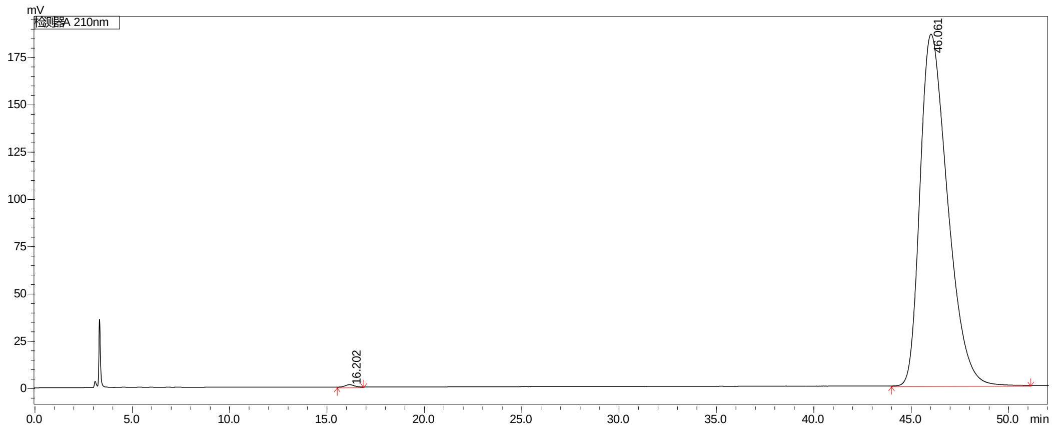
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	16.369	958071	30247	5.912	5.912
2	46.410	15248505	155507	94.088	94.088

R-**2 (After recrystallization)**



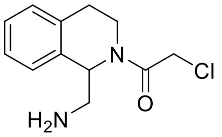
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	16.276	25294	839	0.105	0.105
2	45.986	23951712	244203	99.895	99.895

R-**2 (Up-scale)**

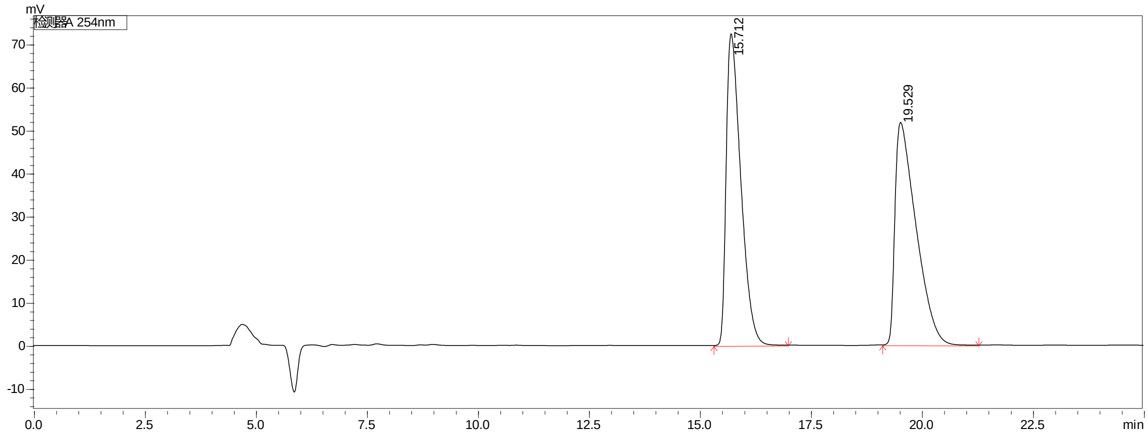


Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	16.202	39391	1275	0.215	0.215
2	46.061	18283699	185881	99.785	99.785

1-(1-(aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-chloroethan-1-one (**3**)

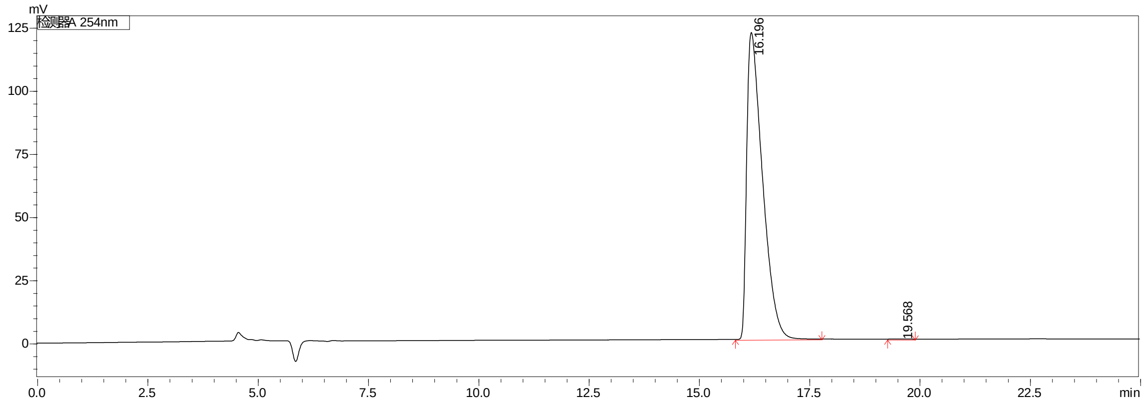


Racemic **3**



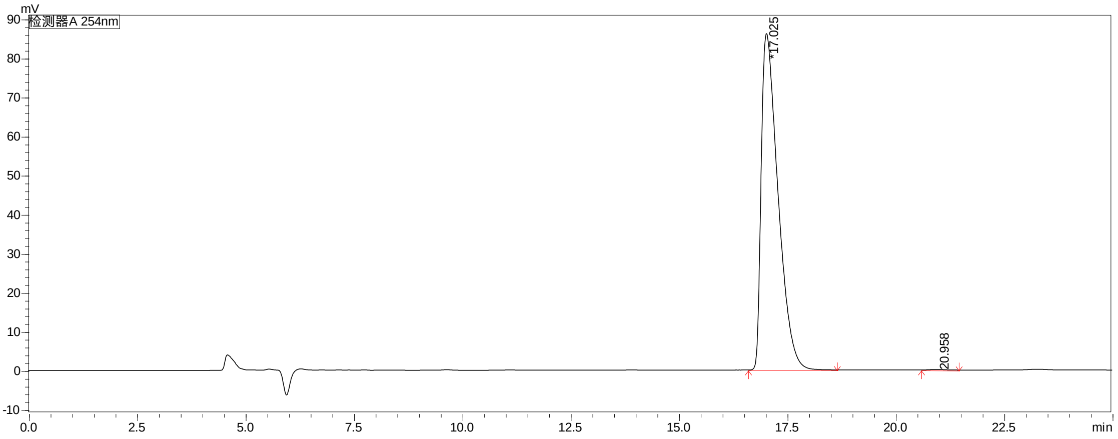
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	15.712	1658927	72351	49.347	49.347
2	19.529	1702853	51659	50.653	50.653

R-**3**



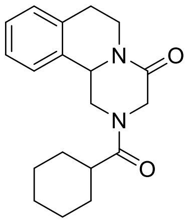
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	16.196	3022533	121464	99.949	99.949
2	19.568	1547	82	0.051	0.051

R-**3 (Up-scale)**

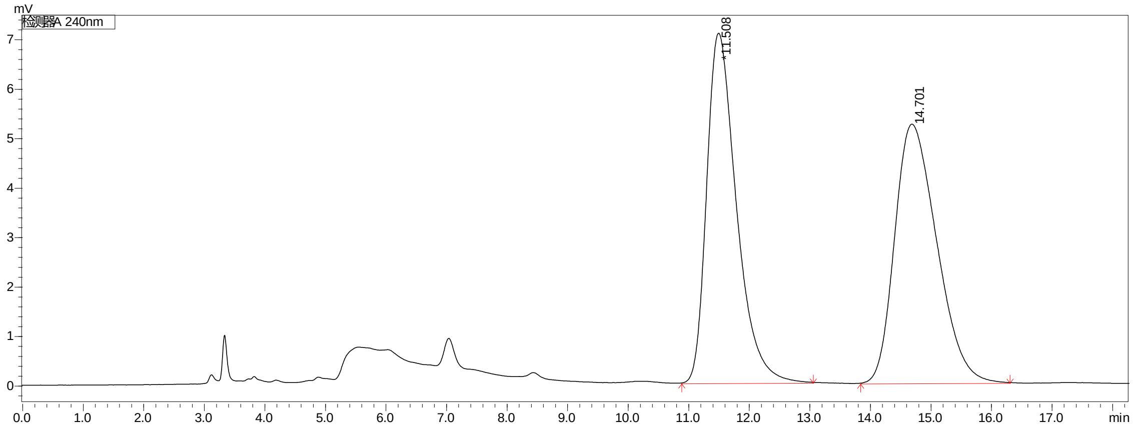


Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	17.025	2322273	86147	99.854	99.854
2	20.958	3399	147	0.146	0.146

(R)-2-(cyclohexanecarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one (***R*-PZQ**)

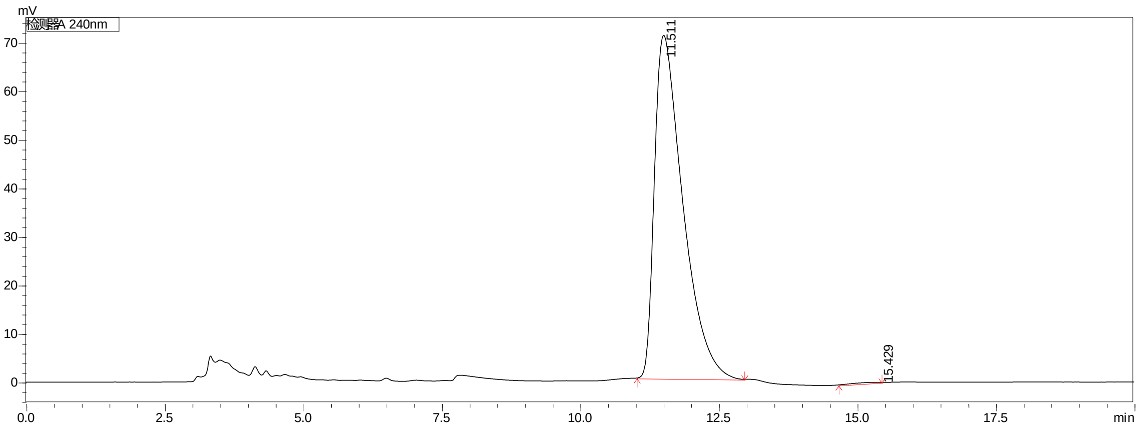


Racemic **PZQ**



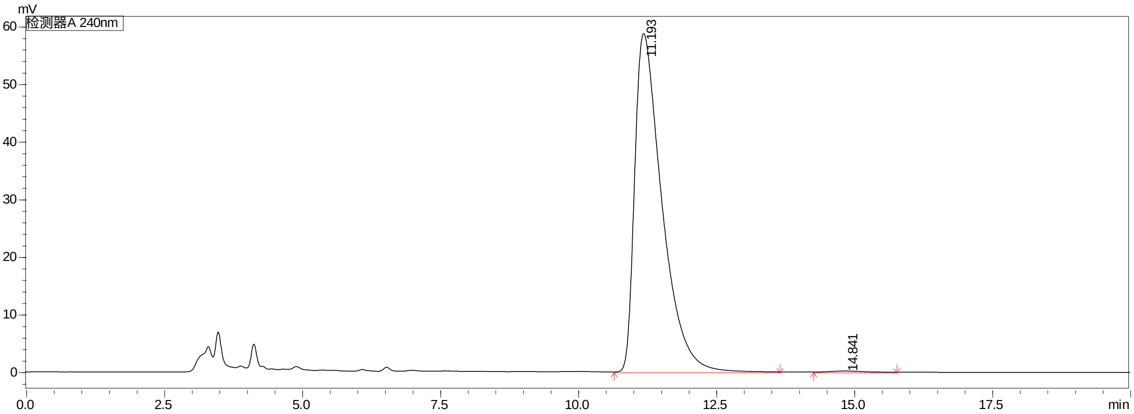
Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	11.508	240958	7069	48.899	48.899
2	14.701	251805	5234	51.101	51.101

R-**PZQ**



Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	11.511	2522316	70695	99.836	99.836
2	15.429	4135	3	0.164	0.164

R-**PZQ (Up-scale)**



Peak #	RetTime (min)	Area (mV*s)	Height (mV)	Conc. (%)	Area (%)
1	11.193	2014501	58729	99.663	99.663
2	14.841	6809	186	0.337	0.337

6. References

[1] W. P. Gallagher, M. Marlatt, R. Livingston, S. Kiau, J. Muslehiddinoglu, *Org. Process Res. Dev.*, 2012, **16**, 1665−1668.

[2] R. C. Schoenfeld, D. L. Bourdet, K. A. Brameld, E. Chin, J. de Vicente, A. Fung, S. F. Harris, E. K. Lee, S. L. Pogam, V. Leveque, J. Li, A. S.-T. Lui, I. Najera, S. Rajyaguru, M. Sangi, S. Steiner, F. X. Talamas, J. P. Taygerly, J.-P. Zhao, *J. Med. Chem.*, 2013, **56**, 8163−8182.