Matrine-Family Alkaloids: Versatile Precursors for Bioactive Modifications

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Abstract: Matrine-family alkaloids as tetracycloquinolizindine analogues from tradition chinese medicine *Sophora flavescens Ait*, *Sophora subprostrata* and *Sophora alopecuroides L* possess various pharmacological activities and have been aroused great interests over the past decades. Especially, plenties of derivatives from matrine-family alkaloids have been synthesized and investigated for their biological activities and encouraging results have continuously acheived in recent several years. These studies are helpful to develop more potent candidates or therapeutic agents and disclose their molecular targets and mechanisms. This review mainly introduces recent advances on the bioactive modifications of matrine-family alkaloids from derivatization at the C-13, C-14 or C-15 position, opening D ring and derivatization, fusing D ring and derivatization and structural simplification based on matrine-family alkaloids.

Keywords: alkaloid; matrine-family alkaloid; sophoridine; matrine; bioactive modification

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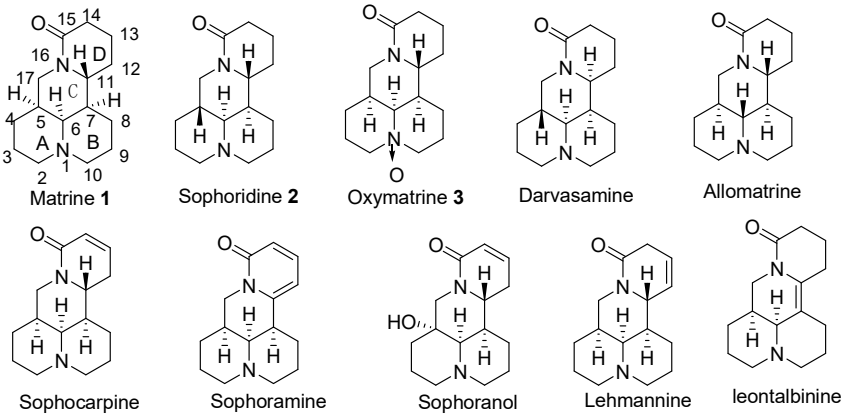
1. Introduction

Sophora species as traditional chinese herbs are widely distributed in Asia, Oceanica, and the Pacific regions and have been utilized in treatment of various diseases such as viral hepatitis, skin, cancer and cardiac diseases for thousands of years[1-5]. Matrine and its analogues as very important active ingredients belong to tetracycloquinolizindines isolated from the roots of Sophora flavescens (Kushen) [6-8]. At present, matrine-family alkaloids have been regarded as ideal lead compounds for the development various bioactive drugs through structural modifications or semisynthesis in view of their excellent properties including special scaffold, flexibility structure, higher solubility as well as stability and good safety profiles[9,10].

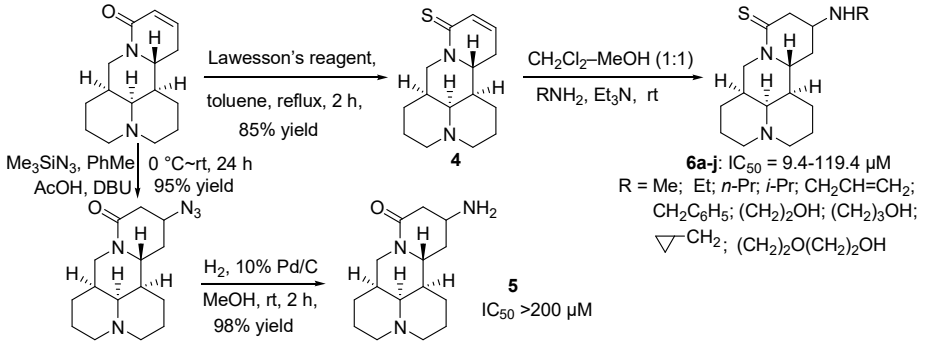
Structural types of matrine-family alkaloids mainly consist of matrine, sophoridine, oxymatrine, darvasamine, allomatrine, sophocarpine, sophoramine, sophoranol, lehmannine and leontalbinine etc (Scheme 1). Matrine-family alkaloids possess extensive pharmacological effects, for example, matrine dispayed multiple bioactivites and therapeutic potentials including antiinflammatory[11-13], antiviral[14-16], antiasthma[17], antiparasitic[18,19], antimicrobial[20], antiarrhythmic[21], antidiuretic[22], antitumor[23-26], immunosuppressive[27-29], neuroprotective[30-32] and cardioprotective [33,34]. Matrine-family alkaloids were also used as surface-imprinted material for molecular selective recognition[35-37] or as amperometric sensor in electroanalytical chemistry[38-40]. However, Matrine-family alkaloids only exhibited moderate activities in most cases, and their studies on smeisynthesis and structural modifications have always aroused immense attention from medicinal scientists. Smeisynthetic and bioactive progresses based on matrine, sophoridine and oxymatrine have successively been reviewed in the early stages [41-43]. Various encouraging results in the field of antiinflammatory, antiviral, antitumor, antiparasitic and other activities had been acheived over the past several years. These studies are helpful to develop more potent candidates or therapeutic agents and further deepen the understanding of their molecular targets and mechanisms. The critical account mainly review recent advances in bioactive modifications of matrine-family alkaloids from derivatization of C-13, C-14 or C-15 position, opening D-ring and derivatization, fusing D-ring and derivatization, structural simplification using matrine-family alkaloid as template.



Scheme 1 Structural types of matrine alkaloids

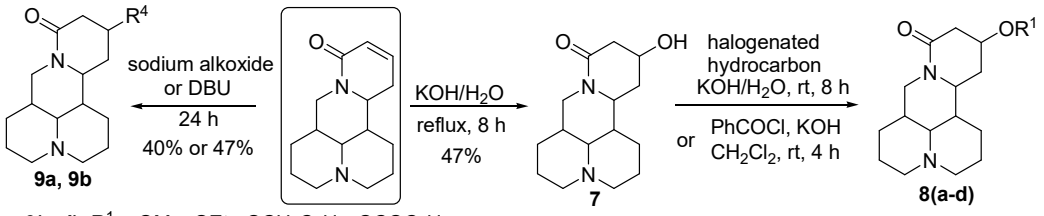
2. Derivatization of C-13 position

The introduction of appropriate group at the C-13 and C-14 position of matrine-family alkaloids was simple and efficient structural modified strategies. In 2010, a series of matrine derivatives with various amino group at the 13-position were prepared (Scheme 2) and their inhibitory activities against pro-inflammatory cytokines (TNF-α) and nuclear factor-kappa B (NFκB) were investigated [44]. The derivative **6a-j** exhibited more potent inhibitory activity against TNF-α with IC_{50} value of 9.4-119.4 μM. Among these compounds, compound **6f** (R = $CH_2CH{=}CH_2$) showed the strongest activity against TNF-α with IC_{50} value of 9.4 μM, but compound **5**, matrine and sophoramine displayed poor inhibition effects with IC_{50} value of >200 μM under the same conditions. The introduction of amino groups to the 13-position of matrine could effectively improved the bioactivities and sulfur atom instead of oxygen atom at the 15-carbonyl had significant effect toward inhibitory activities in vitro.



Scheme 2 Matrine derivatives with various amino group against pro-inflammatory cytokines

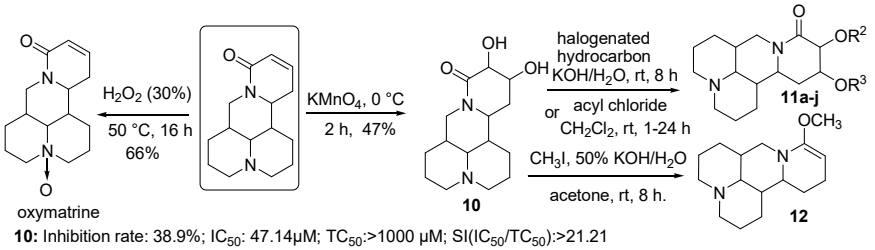
Heat-stress cognate 70 (Hsc70) as a novel target against hepatitis B virus (HBV) plays an important role on the replication for HBV. In 2011, Jiang, Song and coworkers[45] developed types of matrine analogues with substituents at the 13 or 14 position (Scheme 3 and Scheme 4) and investigated their activity on Hsc70 mRNA expression. Most of compounds exhibited down-regulating Hsc70 mRNA expression with real-time RT-PCR method. Compound **11f** (R^2 = OH, R^3 = $OCOCH_2Cl$) exhibited the strongest Hsc70 down-regulatory activity with 88.2 % of inhibition in HepG2.2.15 cells. Among examined analogues, compounds **8b** (R^1 = OEt) and **11f** exhibited more potential anti-HBV activity and low toxicity with SI values were 50.3 and 79.1 respectively. The preliminary SAR indicated that (i) reducing electron density on the ring D is good for the activity of anti-HBV and (ii) introducing electron-withdrawing groups at the 13- and/or 14-position(s) might efficiently improve the activity.



9a, 9b **7** **8(a-d)**

6(a-d): R^1 = OMe; OEt; $OCH_2C_6H_5$; $OCOC_6H_5$
Inhibition rate: 24.7~74.1%; IC_{50}:9.55~120.9 μM; TC_{50}:135.7~1105.3 μM; SI(IC_{50}/TC_{50}):9.14~50.34
9(a-b): R^4 = CH_2NO_2; $NHCH_3$
Inhibition rate: 35.8, 40.1%; IC_{50}:54.45,167.73 μM; TC_{50}:>1000, >1000 μM; SI(IC_{50}/TC_{50}):>18.36, >5.96
positive control **PFA:** IC_{50}: 106.3 μM; TC_{50}: >1000 μM; SI(IC_{50}/TC_{50}): >9.41

Scheme 3 Matrine analogues with substituents at the 13 position against hepatitis B virus



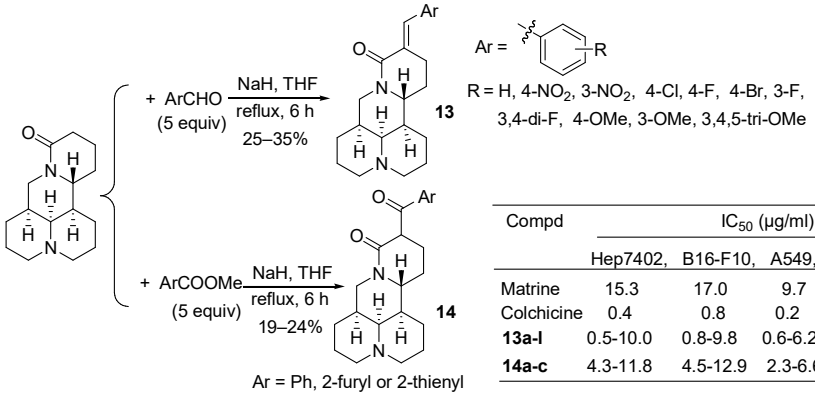
oxymatrine **10** **11a-j** **12**

10: Inhibition rate: 38.9%; IC_{50}: 47.14μM; TC_{50}:>1000 μM; SI(IC_{50}/TC_{50}):>21.21
11a-j: R^2 = OCH_3, OBn, OCOEt, $OCO(4\text{-F-}3\text{-}NO_2)C_6H_3$, OH,
R^3 = OCH_3, OBn, OCOEt, $OCO(4\text{-F-}3\text{-}NO_2)C_6H_3$, $OCOCH_3$, $OCOCH_2Cl$, $OCOCHClCH_3$, $OCOC_6H_5$, $OCO(4\text{-F-}3\text{-}NO_2)C_6H_3$
Inhibition rate: 34.5~88.2%; IC_{50}: 2.76~120.9 μM; TC_{50}: 37.04~1104.83 μM; SI(IC_{50}/TC_{50}): 1.69~79.14
12: Inhibition rate: 39.7 (0.16
positive control **PFA:** IC_{50}: 106.3 μM; TC_{50}: >1000 μM; SI(IC_{50}/TC_{50}): >9.41

Scheme 4 Matrine analogues with substituents at the 14 position against hepatitis B virus

3. Derivatization of C-14 position

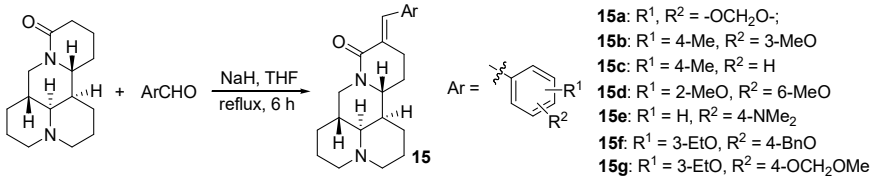
In 2012, a series of compounds based on the modifications matrine of C-14 position were synthesized and assayed their antitumor activities in vitro (Scheme 5)[46]. All these compounds **13** and **14** displayed more potent antitumor activities than that of the parent matrine in the tested cancer cells, and compound **13i** (R = MeO) showed the strongest anti-proliferative activities toward Hep7402, B16-F10, A549 and TW03 four human cancer cell lines (IC_{50} = 0.5 μg/ml, 0.8 μg/ml, 0.6 μg/ml and 1.2 μg/ml), and its activities were near to that of positive control colchicine with IC_{50} value of 0.4 μg/ml, 0.8 μg/ml, 0.2 μg/ml and 1.3 μg/ml. The results comfirmed that the C-14 position modifications of matrine type of alkaloids might be efficient for the development of novel potent antitumor agents.



Compd	IC_{50} (μg/ml)			
	Hep7402,	B16-F10,	A549,	TW03
Matrine	15.3	17.0	9.7	16.3
Colchicine	0.4	0.8	0.2	1.3
13a-l	0.5-10.0	0.8-9.8	0.6-6.2	1.2-6.4
14a-c	4.3-11.8	4.5-12.9	2.3-6.6	2.4-8.1

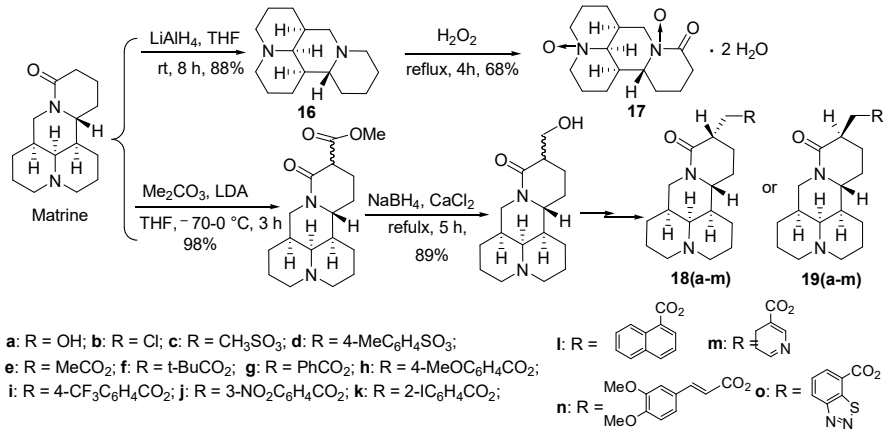
Scheme 5 Anti-tumor activities of matrine derivatives based on the modifications of C-14 position

In 2016, eight derivatives from the modification of the C-14 position of sophoridine were synthesized and their antiproliferative activity against five human tumor cell lines (A549, KB, KB-VIN, MDA-MB-231 and MCF7) were investigated (Scheme 6)[47]. However, the results demonstrated that the strategy was not effective and most of these derivatives exhibited poor anticancer activity, derivative **15f** showed the most potent inhibitory activity toward five human tumor cell lines with IC_{50} value of 17.6-27.9 μM and IC_{50} value of the control drug paclitaxel (PXL) was 0.00003-2.6 μM.



Scheme 6 Anti-tumor activities of sophoridine derivatives from the C-14 position modifications

Types of derivatives from matrine were synthesized and assayed them against bacco mosaic virus (TMV), fungicidal and insecticidal activity (Scheme 7)[48]. All these compounds, compounds **18a**, **19g** and **19o** showed more potent inhibitory activity against TMV. Especially, compounds **19o** demonstrated the most potency toward TMV with inhibitory rate of 74.6% in vitro, 76.9%, 72.3% and 75.7% (inactivation, curative, and protection activities) in vivo at 500 μg/mL. The inhibitory rate of positive drugs ribavirin and NK-007 were 40.8%, 37.5%, 38.2%, 37.7% and 70.3%, 66.1%, 68.4%, 67.5% at 500 μg/mL (Table 1) under the same conditions, respectively. These derivatives and their parent matrine still demonstrated a broad spectrum fungicidal activities against 14 kinds of plant pathogens. For example, compound **19o** showed the most potent activity against *Phytophthora capsici Leonian* with the inhibition rate of 96.4% under 50 μg/mL. All these compounds also displayed satisfactory insecticidal activity toward *Mythimna Separate, Helicoverpa Armigera, Ostrinia Nubilalis, Plutella xylostella, and Culex Pipiens Pallens*. The inhibition rate of compound **19g** against *C. Pipiens Pallens* reached 70% at a concentration of 1 μg/mL

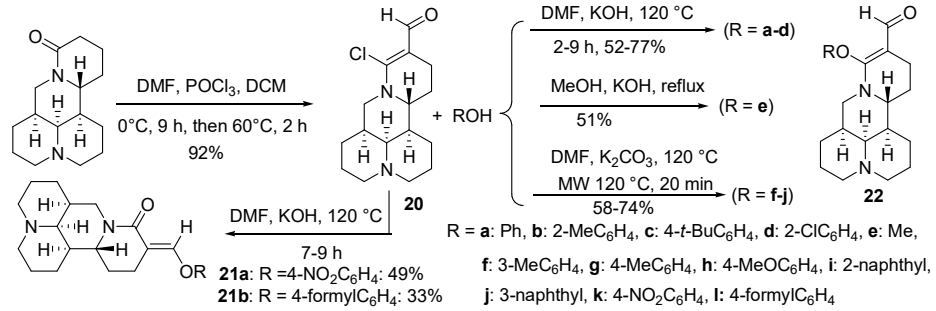


Scheme 7 Bacco mosaic virus (TMV), fungicidal, and insecticidal activity of matrine analogues

Table 1 Antiviral activities ofmatrine analogues against TMV and in Vivo

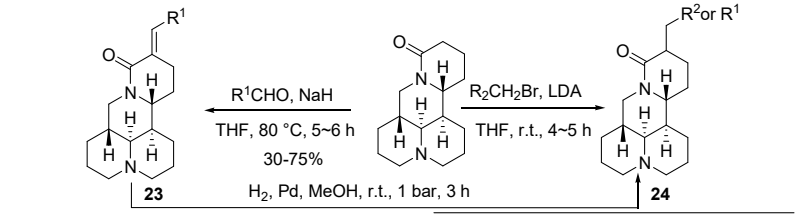
		In Vitro	in Vivo		
compd	Conc μg/ml	Inhibition rate (%)	inactivation effect (%)	curative effect (%)	protection (%)
Matrine	500	44.7	45.7	42.8	44.4
	100	21.5	18.9	15.6	20.5
Ribavirin	500	40.7	38.5	36.0	39.8
	100	9.6	8.4	13.9	11.3
NK-007	500	65.4	67.8	66.9	70.2
	100	21.9	25.8	23.7	28.0
16	500	52.3	49.2	50.0	48.7
	100	27.2	22.5	30.0	28.0
17	500	37.3	40.0	43.5	36.4
	100	12.0	15.9	18.4	7.7
18(a-m)	500	31.9-67.3	36.8-69.5	36.1-65.8	31.5-63.0
	100	0-27.2	0-32.0	0-30.0	0-30.9
19(a-m)	500	36.0-74.6	40.0-76.9	35.9-72.3	36.4-75.7
	100	0-34.1	4.6-34.1	5.9-29.0	0-32.2

Xu and coworkers[49] synthesized types of matrine derivatives with 14-formyl-15-aryloxy /methoxy or 14-aryloxymethylidenyl and evaluated for their oral toxicity against two widely distributed and serious typical lepidopteran insect pests *M. separata and P. xylostella* (Scheme 8). The potent oral toxicity of these derivatives as well as matrine and toosendanin (a positive control) against *P. xylostella* treated at 20 mg/larvae was investigated. All the derivatives exhibited potent oral toxicity toward *M. separata* after 48 h with mortality rates of 32.1-42.8%, whereas the mortality rates of matrine and toosendanin was 28.5% and 46.4%, respectively. Particularly, compounds **21a**, **21b** and **22j** demonstrated more insecticidal potency than that of the parent compound and positive control toosendanin and corrected mortality rate of **21a**, **21b**, **22j**, matrine and toosendanin against *M. separata* on leaves after 35 day were 62.1%, 55.2%, 58.6%, 24.2% and 48.3%. Interesting results based on structure–activity relationships could demonstrate that the introduction of an electron-withdrawing group on the phenyl ring (for example **21a**) could increase insecticidal activity and a polycyclic aromatic hydrocarbonoxy at the C-15 position of **20** generated more potent pesticidal agents.



Scheme 8 Matrine ether derivatives as insecticidal agents

Types of α,β-unsaturated sophoridinic derivatives were designed and synthesized through comparison with structure of sophoridine and chalcone and their cytotoxicity against HepG-2 and CNE-2 cell lines in vitro were investigated using MTT assay (Scheme 9)[50]. All these derivatives exhibited more potent anti-proliferative activities than that of sophoridine. Compounds **23e** (R^1 = *t*-BuC_6H_4) and **23k** (R^1 = 2-(3-Mefuryl)) showed the most potency against HepG-2 and CNE-2 cell lines with IC_{50} of 35.1, 38.3 μM and 25.5, 33.8 μM, but not such as control drug Taxo (IC_{50} = 15.6 and 0.18 μM). Studies on molecular docking contributed to the understanding at the docking in the active site of DNA–Topo I complex and the mode of binding.



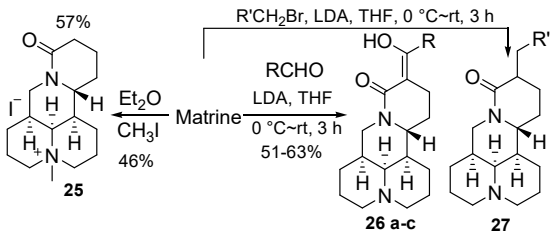
R^1 = *n*-Bu, C_6H_5, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-ClC_6H_4, 2-naphthyl, 2-furyl, 2-thienyl, 2-(4-Clthienyl), 2-(4-Methienyl), 2-(3-Methienyl)

R^2 = Me, *n*-Bu, pentyl, C_6H_5, 2-furyl, 2-thienyl

Compd	IC_{50} (μM) HepG-2	CNE-2
23	25.5~> 100	33.8~> 100
24	57.8~> 100	83.1~> 100
Sophoridine	4670	5379
Taxo	15.6	0.18

Scheme 9 Anti-cancer activities of novel α,β-unsaturated sophoridinic derivatives

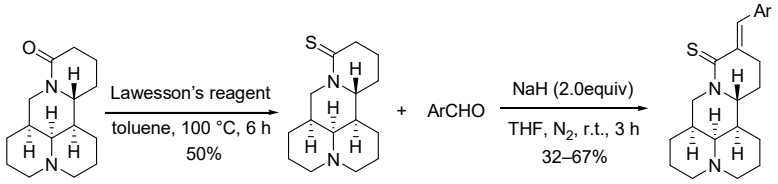
In 2017, Wang group[51] synthesized five matrine derivatives and assayed their anti-proliferation activity against four human cancer cell lines A549, BT20, MCF-7 and U20S cells in vitro (Scheme 10). Compared with the parent matrine, three compounds of substituted at the 14 position **26a-c** showed more potent activities toward four human cancer cell lines, and compound **26c** exhibited the strongest antiproliferation activity with IC_{50} value of 15.5-16.7 μM. Studies in depth confirmed that compound **26c** arrested cell cycle in the G1 phase in A549 lung cancer cells and significantly induced apoptosis via generation of ROS in a dose-dependent manner. The study provided further information for the development of novel potent antitumor agents through the structural modifications of matrine derivatives.



Compd	R or R'	IC50 (μM) BT20	A549	MCF7	U20S
Matrine	--	301.6	425.3	216.5	152.0
25	--	495.5	353.9	204.5	189.1
26a	naphth-2-yl	136.6	117.9	126.1	85.1
26b	6-MeO-naphth-2-yl	147.0	183.4	112.3	85.2
26c	6-Br-naphth-2-yl	16.7	15.5	15.9	16.4
27	3-MeOC$_6$H$_4$	260.5	247.6	231.6	189.0

Scheme 10 Five matrine derivatives and their anticancer activities

In 2018, Wang group[52] developed a series of thiomatrine derivatives with substitution of the 14 position and their cytotoxicity toward human cancer cell lines in vitro were assayed employing MTT assay (Scheme 11). Compound **28a** (Ar = 3,4-diMeO-naphth-1-yl) exhibited more potent activities against human cancer cell lines of HepG2, SMMC-7721, A549 and CNE2 with IC_{50} values of 9.1, 9.0, 11.4 and 7.8 μM, its anticancer activities were higher than that of matrine and close to the positive Cisplatin (IC_{50} = 8.4, 6.0, 8.5 and 3.8 μM). Cell cycle and induction apoptosis analysis in SMMC-7721 and CNE2 cells indicated that compound **28a** could induce cancer cell cycle arrest and apoptosis in a dosedependent manner. The mechanism studies on induced cancer cell apoptosis disclosed that compound **28a** efficiently enhanced expression of cleaved caspase-3 and reduced the levels of of Bcl-2/Bax.

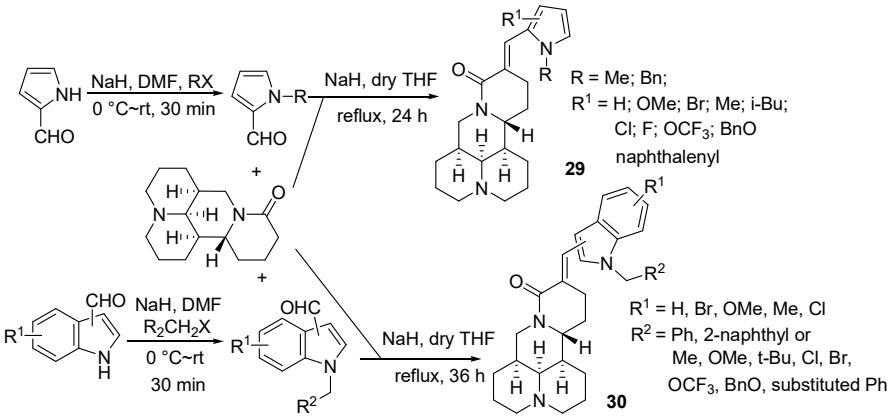


Ar = substituted Ph; 2-furyl; substituted 2-furyl; 2-thienyl, 4-pyridyl; naphthalen-1-yl; naphthalen-2-yl; 4-quinolinyl; 1,4-benzodioxin-6-yl; substituted naphthalen-1-yl; substituted naphthalen-2-yl; 9-anthryl

Compd	IC_{50} (μM) HepG2	SMMC-7721	A549	CNE2
28	9.1	9.0	11.4	7.8
Matrine	4178	5591	5725	5278
Cisplatin	8.4	6.0	8.5	3.8

Scheme 11 Thiomatrine derivatives as potential anticancer agents

Recently, Wang group[53] prepared a series of 14-(N-substituted-2-pyrrolemethylene) and 14-(N-substituted-indolemethylene) matrine derivatives and investigated their potent cytotoxicity against SMMC-7721, A549 and CNE2 using MTT assay (Scheme 12). All the target compounds exhibited more potent cytotoxicity against three human cancer cell lines SMMC-7721, A549 and CNE2 than that of the parent compound matrine (Table 2). For example, compound **29a** (R = Bn, R^1 = 3,5-diMeO) and **30a** (R^1 = 3-MeO, R^2 = 3-ClC$_6$H$_4$) displayed the strongest potency toward SMMC-7721, A549 and CNE2 with IC_{50} values of 4.65, 8,05, 3.55 μmol/L and 3.95, 4.96, 3.42 μmol/L, respectively. The IC_{50} values of positive drug cisplatin was 6.08, 8.56 and 3.89μmol/L under the same conditions. The Annexin V-FITC/PI dual staining assay demonstrated that compounds **29a** and **30a** could efficiently induce the apoptosis of SMMC-7721 and CNE2 cells with a dose-dependent manner. The cell cycle results still confirmed which compound **29a** might result in cell cycle arrest of SMMC-7721 and CNE2 cells to stay at G2/M phase.

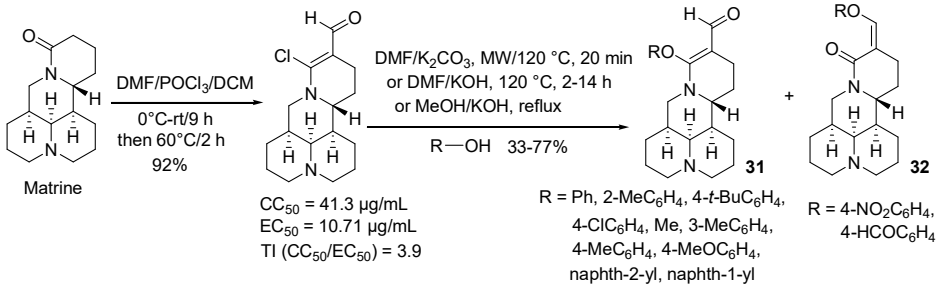


Scheme 12 Design and synthesis of a series of 14-substituted matrine derivatives

Table 2 The anti-proliferative activities of matrine derivatives 29 and 30.

Compd.	Cytotoxicity IC_{50} (μmol/L)		
	SMMC-7721	A549	CNE2
29	4.65~>100	8.05~>100	3.55~>100
30	3.26~28.21	4.96~>50	3.42~17.43
Matrine	6591	5725	5278
Cisplatin	6.08	8.56	3.89

The exploring and development of novel, high selective and safe drugs for the treatment of HIV/AIDS has always attracted much attention over the past several decades. In 2018, 14-Formyl-15-aryloxy/methoxymatrine and 14-aryloxymethylidenyl-matrine derivatives were synthesized and their potent acivities against HIV-1 (Scheme 13) were investigated[54]. The 50% of cytotoxic and effective concentration (CC_{50} and EC_{50}) as well as therapeutic index (TI) of these derivatives were respectively showed in Table 3. All these derivatives showed the corresponding activity and compound **31j** (R = naphth-1-yl) exhibited the most potency against HIV-1_{IIIB} replication in acutely infected C8166 cells with EC_{50} and TI values of 1.79 μg/mL and 98.2. Compared with the positive drug AZT, all these compounds showed poorer activities toward HIV-1, but these studies provided a new pathway for the development of novel HIV-1 inhibitors via further structural modification and application of matrine.



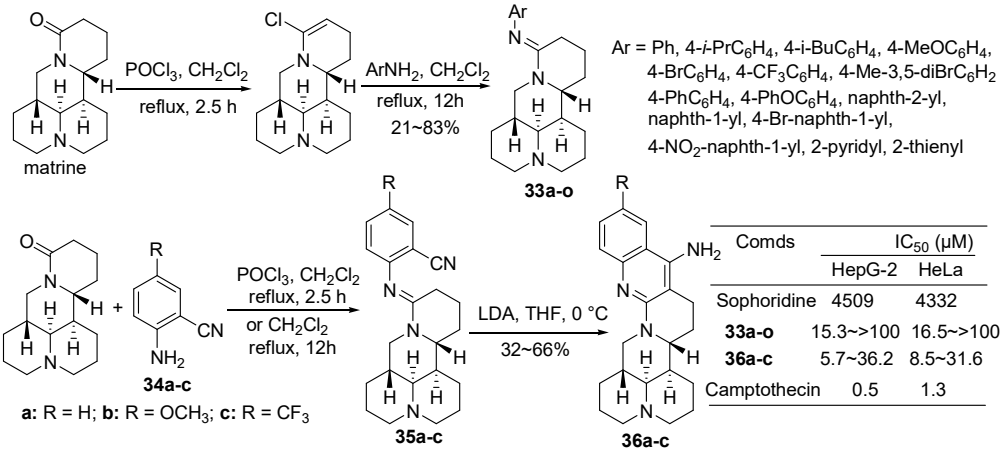
Scheme 13 A series of 14-substituted matrine derivatives with acivities against HIV-1

Table 3 Potent acivities against HIV-1 of a series of 14-substituted matrine derivatives

Compounds	R	CC_{50} (μg/mL)	EC_{50} (μg/mL)	TI (CC_{50}/EC_{50})
matrine	--	>200	>200	inactive
2	--	41.3	10.71	3.9
31a-j	--	56.87->200	1.79-61.17	2.1-98.2
32a	4-$NO2C_6H_4$	97.96	14.36	6.8
32b	4-$HCOC_6H_4$	98.97	48.26	2.1
AZT	--	1291	0.00251	514342.6

4 Derivatization of C-15 position

Recently, types of derivatives from sophoridine imine were synthesized and their anticancer activity in vitro based on the binding mode of camptothecin with Topo I were investigated[55]. Compared with positive drug camptothecin, all these derivatives exhibited lower potent activity against HepG-2 and HeLa cell lines (Scheme 14). The strongest activity of compound **36b** (R = OMe) showed anti-proliferative activities toward HepG-2 and HeLa cell lines with IC_{50} values of 5.7 μM and 8.5 μM. Molecular docking analysis demonstrated that the formation π-π stacking interaction with DNA Topo I through the introduction of conjugated planar structure resulting in enhancing of biological activity. The mechanism was inhibition of the activity of DNA Topo I and induction of cell cycle arrest at the G0/G1 phase to cause apoptotic cell death. The studies provided an efficient pathway for the development of novel Topo I inhibitor via structural optimizations active lead compounds.

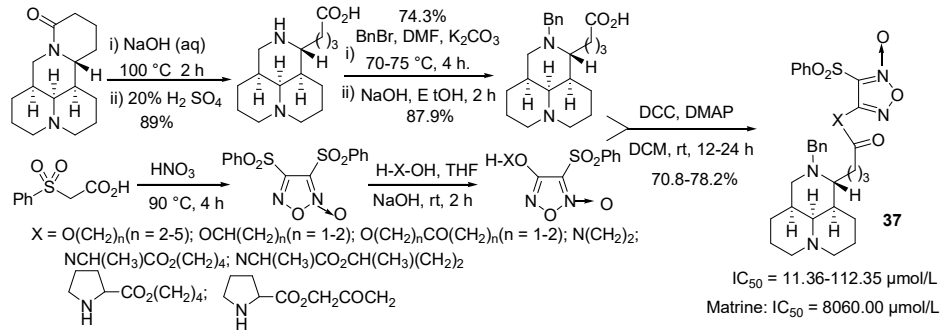


Scheme 14 Anticancer activities of sophoridinic imine derivatives

5. Opening D ring and derivatization

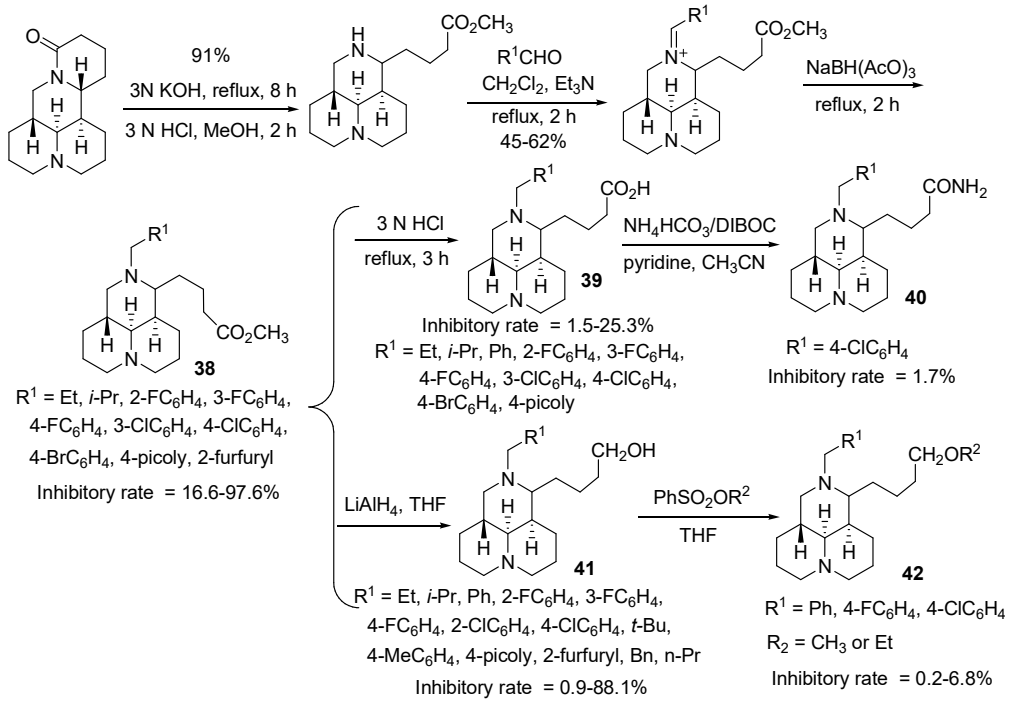
In 2010, Zhang and coworkers[56] synthesized nitric oxide donor-based matrine derivatives and investigated their anticancer activity against hepatocellular carcinoma cells (HepG2 cells). All the derivatives displayed expectedly anticancer activity against HepG2 cells, and compounds **37a** (X = $O(CH_2)_2$), **37b** (X = $O(CH_2)_3$), 37**c** (X = $OCH(CH_3)CH_2$) and **37h** (X = $O(CH_2)_2O(CH_2)_2$) exhibited more potency toward HepG2 cells with IC_{50} value of 11.36, 11.45 and 14.56 and 14.21

μmol/L than that of positive control 5-fluorouracil with IC_{50} value of 15.92 (Scheme 15). In general, the activity of derivatives was related with the length of carbon chain, and 2-3 carbon was good for the anticancer activity.



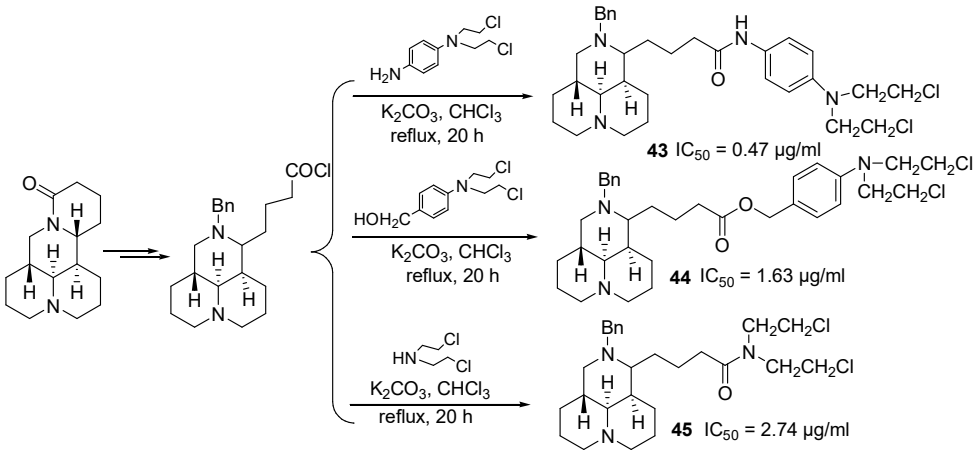
Scheme 15 Anti-cancer activity of nitric oxide donor-based matrine derivatives

In 2014, Song group[57] synthesized series of N-substituted sophoridinic acid derivatives and evaluated for their cytotoxicity activities against six human tumor cell lines (colon cancer HepG2 and HCT116, lung cancer H1299, malignant glioma U87, breast cancer MCF-7 and nasopharyngeal epidermoid carcinoma KB). All these derivatives were firstly investigated their antiproliferative activities in human HepG2 hepatoma cells using MTT assay. Compound **38g** (R^1 = 4-ClC_6H_4), **38h** (R^1 = 4-BrC_6H_4), **41c** (R^1 = *t*-Bu), **41j (**R^1 = 2-ClC_6H_4**)** and **41k**(R^1 = 4-ClC_6H_4) displayed more potent cytotoxicity activities with inhibitory rate of 97.6%, 89.6%, 95.7%, 88.1% and 87.7% and inhibitory rate of control drug TPT was 72.6% (Scheme 16). Compounds **38g** and **41k** also exhibited similar cytotoxicities (IC_{50} = 4.05-20.02 μM and 4.52-10.64 μM) against six human tumor cell lines with TPT (IC_{50} = 3.28-16.60 μM). The mechanism studies demonstrated \compound **41k** efficiently inhibited the activity of DNA topo I and followed to arrest the cell cycle at G0/G1 phase. However compound **38g** had no apparent inhibitory activity of Top I at the concentration of 15 mg/ml. Compounds **38g** and **41k** could be considerably safe in vivo through the safety evaluation in rat model.

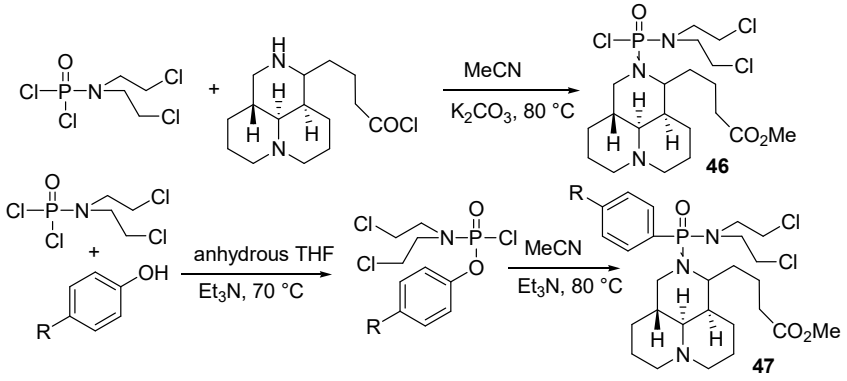


Scheme 16 Novel N-substituted sophoridinol derivatives as anticancer agent

In 2015, Tao group[58] synthesized types of sophoridinic acid derivatives with nitrogen mustard group and assayed their potential anticancer activities (Scheme 17). Derivatives **43** exhibited the most potency against hepatocellular carcinoma with IC_{50} = 0.47 μg/ml and the average inhibitory rates on HepA cancer was 42.45% in vivo. SAR studies indicated the introduction of benzyl group to the nitrogen atom at the C-12 position and nitrogen mustard group with aromatic instead of aliphatic group were helpful to enhance potent antitumor activity. Later, Tao group [59] still designed series of sophoridinic acid analogues with nitrogen mustard or phosphoramide mustard group and evaluated for their topoisomerase (Topo) inhibitory activity and cytotoxicity against tumor cell lines (Scheme 18). All the tested compounds displayed potent cytotoxicity against SMMC-7721, LoVo, MCF-7, K562, S180 and H22 tumor cell lines. Derivatives **47** showed the most potent inhibition activities toward S180 and H22 cell lines with IC_{50} values of 2.01-3.65 μM and 1.01-2.65 μM.



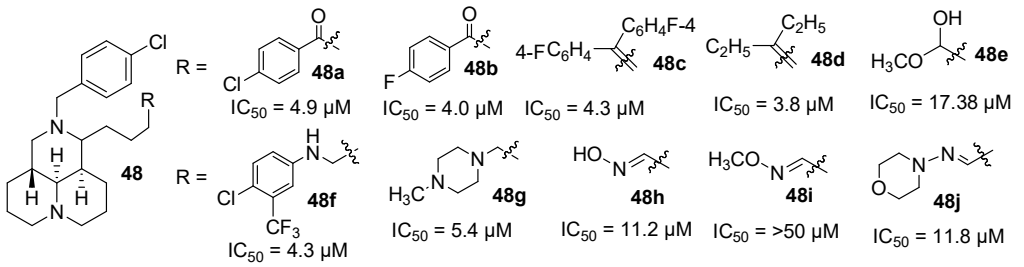
Scheme 17 Novel nitrogen mustard sophoridinic acid derivatives as potential anticancer agents



Compound	IC50 (μM) SMMC-7721	LoVo	MCF-7	K562	S180	H22	L292
46	77.92	77.52	75.98	34.33	10.06	11.7	150.52
47a: R = CH_3	60.80	62.47	61.20	27.07	2.89	2.17	180.66
47b: R = OCH_3	65.16	46.17	38.86	54.50	3.50	2.65	104.30
47c: R = Cl	31.73	33.43	31.92	18.07	2.02	1.01	162.41
47d: R = NO_2	36.51	32.25	34.62	20.31	2.01	1.80	105.32
47e: R = H	77.89	69.95	86.57	32.73	3.65	1.85	138.54

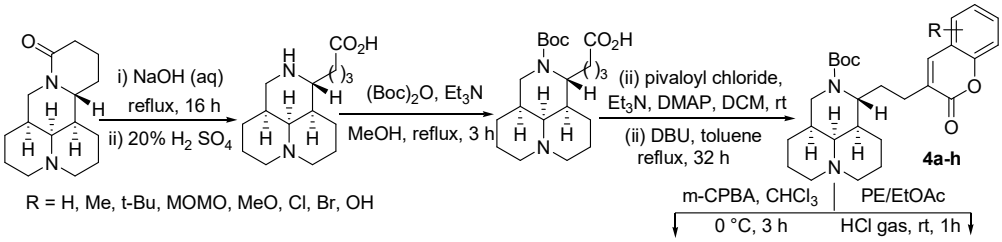
Scheme 18 Novel phosphoramide mustard sophoridinic acid analogues.

In 2016, a series of substituted derivatives at the C-11 position of sophoridinic acid containing sophoridinic ketones, alkenes and amines were synthesized and their antiproliferative activity against human HepG2 hepatoma cell line were investigated employing taxol as a positive control (Scheme 19)[60]. All these derivatives exhibited similar inhibitory activity (IC_{50} = 3.82- > 50 μM) against HepG2 with taxol (IC_{50} = 15.6 μM). Compound **50a** demonstrated a similar mechanism of action to its parent compound sophoridine. These studies provide satisfactory information to develop further novel anticancer candidates via optimizing sophoridinic acid derivatives.



Scheme 19 12-N-*p*-chlorobenzyl sophoridinol derivatives as a novel family of anticancer reagents

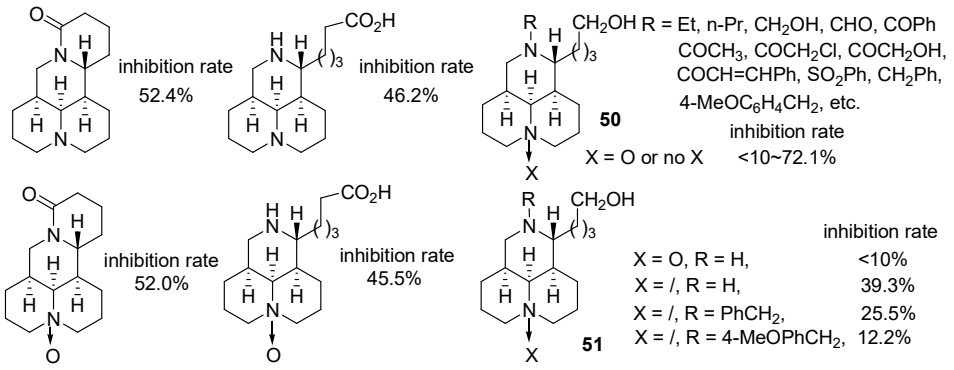
In 2016, a series of matrine derivatives containing benzo-α-pyrone structure were synthesized and their activities against cancer cell lines were assayed [61]. Most of the derivatives exhibited more potent anticancer effects than that of parent matrine, and compound **49i** (R = 6,8-di-*t*-Bu) showed the most potent activities toward SGC-7901, MCF-7, A549 and Bel-7402 with IC_{50} values of 9.4, 7.3, 8.1 and 7.6 μM (Scheme 20). Compounds **49i** could efficiently inhibited cancer cell proliferation through induction G1 cell cycle arrest to down-regulate PI3K/Akt pathway and suppression of autophaghy attenuated with no obvious side effects. The results of active studies in vitro and in vivo indicated that derivatives **49i** might be therapeutic agents for anti-lung cancer.



	IC_{50} (μM)			
	SGC-7901	MCF-7	A549	Bel-740
49a-h	13.2- 71.8	14.2-82.9	18.0->100	15.6-71.1
49i-k	9.4-63.3	7.3-55.5	8.1-89.9	7.6-63.8
49l-q	39.9-94.9	33.3-99.1	52.9->100	40.8-87.8
Matrine	1380	2497	3923	2057

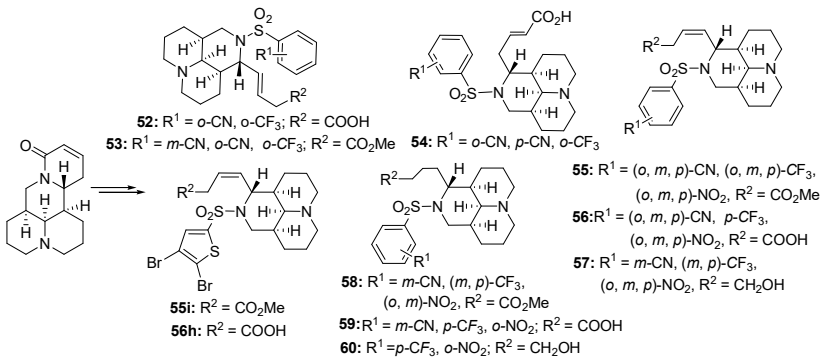
Scheme 20 Anti-lung cancer agents of matrine derivatives containing benzo-α-pyrone structure

Matrine and oxymatrine as natural anti-hepatitis B virus (HBV) agent could efficiently down-regulate host heat-stress cognate 70 (Hsc70) expression and exhibited a special mechanism different from nucleosides. In 2011, Jiang, Song and coworkers[62] developed a series of N-substituted matrinic acid derivatives against HBV using Hsc70 as a target and investigated their regulation of Hsc70 mRNA expression (Scheme 21). Among all these compounds, Compond **50a** (R = *p*-methoxylbenzyl) showed more potent activity against Hsc70 mRNA expression with inhibition rate of 72.1% than that of the parent compound Matrine and oxymatrine. Results based on SAR analysis disclosed that carboxyl group at the 11-pisition side chain was favorable for activity and the introduction of substituted benzyl on the nitrogen atom at the 12-position could extremely enhance the activity.



Scheme 21 N-substituted matrinic acid derivatives as 70 (Hsc70) down-regulators

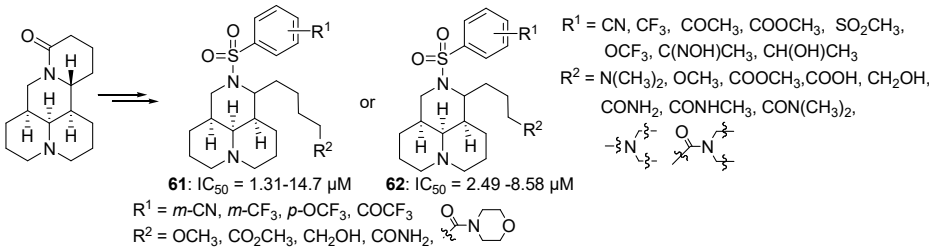
In 2013, Song group[63] found N-substituted sophocarpinic acid derivatives of opening D ring exhibited more potent activities against coxsackie virus B3. Later, the group[64]designed and prepared types of sophocarpinic alcohol, acid or ester derivatives (Scheme 22) and assayed their anti-CVB3 activities through viral cytopathogenic effect (CPE) assay. Sophocarpinic esters **53** showed more potency against anti-CVB3 activities with IC_{50} value of 7.3-11.9 μM and highly cytotoxic activities with TC_{50} value of 38-80 μM in vitro. All of *Z*-sophacarpinic ester derivatives **55** displayed promising activities with IC_{50} values of 1.19-9.24 μM. For example, **56b** (R^1 = *m*-CN) exhibited excellent potency anti-CVB3 with an IC_{50} of 3.07 μM and SI value of 176. Sophocarpinols **57** demonstrated moderate to good potency with IC_{50} value of less than 17.0 μM. Especially, compound **57d** with *o*-NO_2 substituent showed satisfactory potency against CVB3 (IC_{50} = 2.31 μM and SI = 153). These results provided crucial information for the development broad-spectrum coxsackie B virus inhibitors.



Scheme 22 Novel N-benzenesulfonyl sophocarpinol derivatives as coxsackie B virus inhibitors

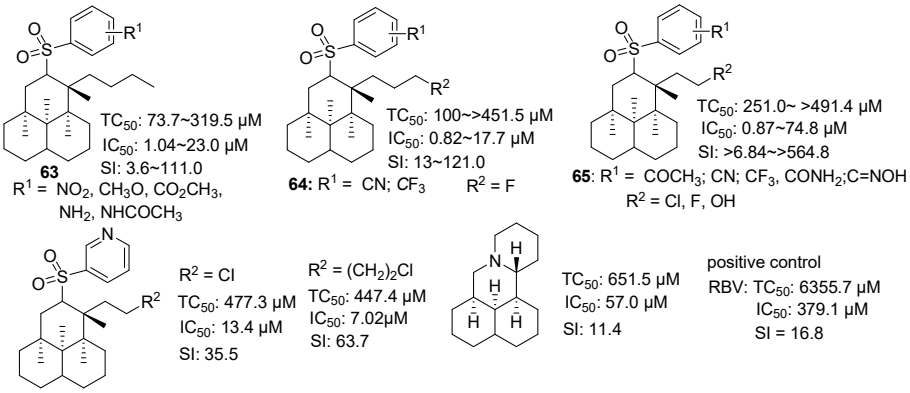
Song group[65] prepared series of derivatives of the opening D ring of matrine such as N-benzenesulfonyl matrinic amine, amide and methyl ether and investigated their antiviral activities against coxsackievirus B3 (CVB3) (Scheme 23). Most of these derivatives exhibited highly antiviral activity in vitro and compound **62f** (R^1 = *m*-CF_3, R^2 = $CONHCH_3$, IC_{50} = 2.56 μM), **62g** (R^1 = *m*-CF_3, R^2 = $CON(CH_3)_2$, IC_{50} = 2.49 μM,) and **62h** (R^1 = *o*-CF_3, R^2 = $CON(CH_3)_2$, IC_{50} = 2.74 μM) displayed more inhibition potency against CVB3 activities with higher selectivity index (SI) of 63.3-67.2. The derivatives with a suitable amido group at the end

of side chain might improve their antivirus potency and a stronger electron-withdrawing group on the phenyl ring the substitution of N-benzenesulfonyl could be helpful to enhance the inhibition against CVB3 activity.



Scheme 23 Structure–activity relationship of N-benzenesulfonyl matrinic acid derivatives

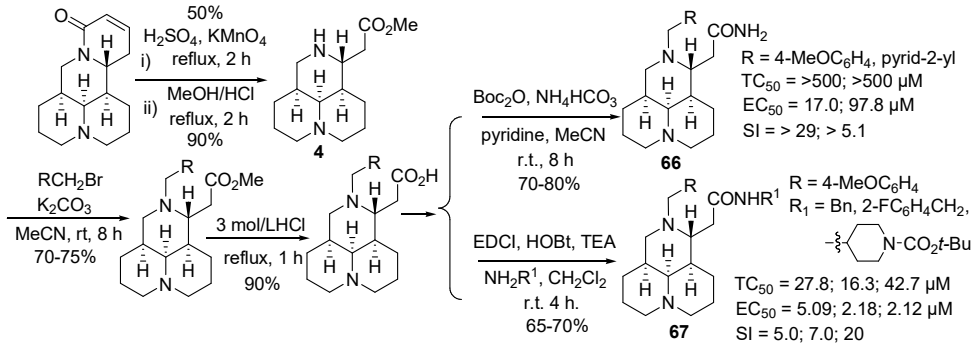
In 2017, Song group[66] still synthesized a series of 12N-benzenesulfonyl matrinic derivatives containing butane and halogenated butane/ethane at the 11 position of side chain and investigated their anti-coxsakievirus activities against CVB3 (Scheme 24). Among these derivatives, compound **63a** (R^1 = *o*-CN) showed broad-spectrum activities against CVB3 with TC_{50}, IC_{50} and SI values of 155.2~>200, 0.69~5.14 μM and >500, respectively. TC_{50}, IC_{50} and SI values of the positive drug RBV were >500, 500~3316.7 μM and 16.8 under the same comditions. Results from SAR analysis indicated the introduction of a fluoro atom on the end of side chain might be favorable for keeping anti-coxsackievirus potency. Compound **63a** still exhibited satisfactory PK profile in oral administration and confirmed that it was a highly druggable nature and could used as a potent anti-coxsackievirus agents.



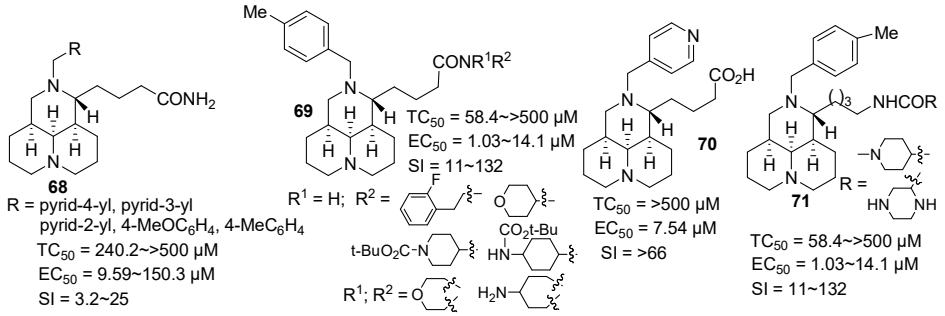
Scheme 24 12N-sulfonyl matrinic butanes as potential anti-coxsackievirus agents

In 2016, Song group[67] synthesized a series of 12-benzyl matrinic amide and ethanamide derivatives employing matrine and sophocarpine as substrates and assayed their anti-HCV activity (Scheme 25 and 26). Compared with positive drug, these derivatives exhibited poorer activity against HCV activity. Compounds **69** showed the most potent anti-HCV activity with EC_{50} and selectivity index (SI) values ranging from 1.03 to 14.1 μmol/L and 11 to 132, and EC_{50} and SI values of positive control telaprevir was 0.02 μmol/L and 1950. Results of SAR demonstrated that the introduction of a suitable group at the N atom end of matrinic amide was helpful to increase anti-HCV activity. Further investigation also confirmed that compound **70** showed satisfactory

drug-like characteristics with an excellent PK and safety profile in vivo.

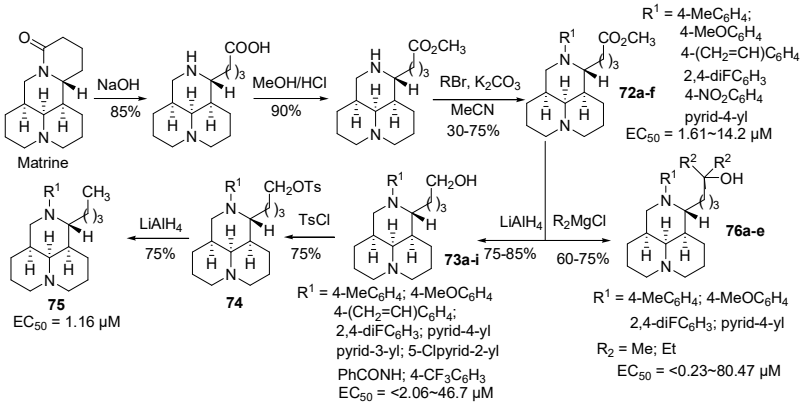


Scheme 2512-benzyl matrinic acetamide derivatives as a novel family of anti-HCV agents

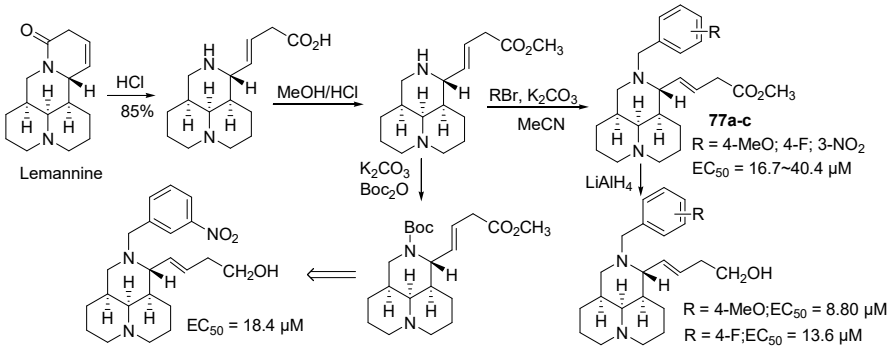


Scheme 26 12-benzyl matrinic butyramide derivatives as a novel family of anti-HCV agents

In 2017, Song group[68] prepared types of 12N-benzyl matrinic derivatives employing matrine and lemanine as lead compound and evaluated for their activity against HCV in Huh7.5 cells (Scheme 27 and 28). However, most of these derivatives showed less potent activity of anti-HCV than that of control drug tala. Compound **73a** demonstrated moderate anti-HCV activity with effective Concentration (EC_{50}) and SI value of 2.81 μM and 136 (EC_{50} and SI value of positive drug Tela was 0.02 μM and 1950). Pharmacokinetic studies demonstrated that Compound **73a** might be used as the potential for oral administration to permit further safety evaluations in vivo. The results of structure–activity relationship indicated that on the benzene ring with electron-donating substitutions was beneficial for the activity, and the unsaturated 11-side chain might not be helpful for the anti-HCV activity.

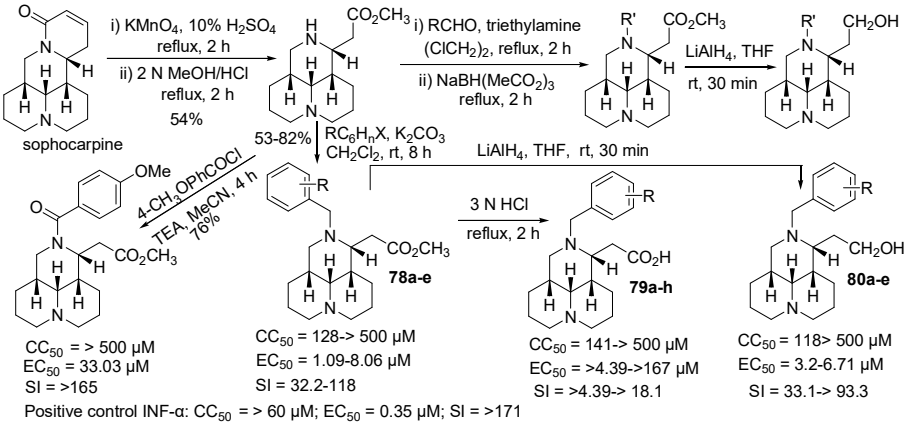


Scheme 27 12N-benzyl matrinic derivatives derivatives as anti-HCV agents



Scheme 28 (Z)-Δβ γ-matrinic crotonols on the 11-side chain as anti-HCV agents

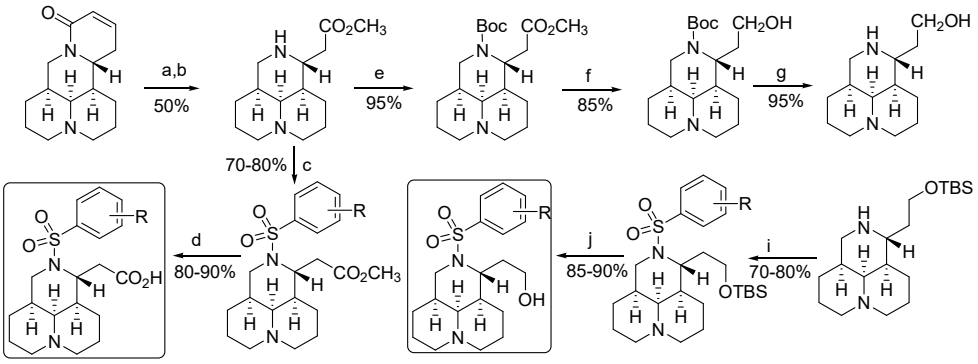
Last year, Types of 12N-substituted matrinic ethanol derivatives[69] were prepared and their antiviral activities against HCV using matrinic acid as lead compound through shorten of the length at the 11 position side chain were investigated (Scheme 29). The results of SAR indicated that there was no significant effect to activity using ethyl chain instituted butyl chain at the 11 position side chain. However, compared with control drug INF-α, most of the derivative exhibited poorer anti-HCV activities. Compound **80a** (R = 4-MeO) showed the most potency toward anti-HCV with EC_{50} and SI value of 3.2 μM and 96.6, and free hydroxyl at the side chain might provide a valuable parent structure to derive and develop for the potential candidate for the treatment of HCV infection.



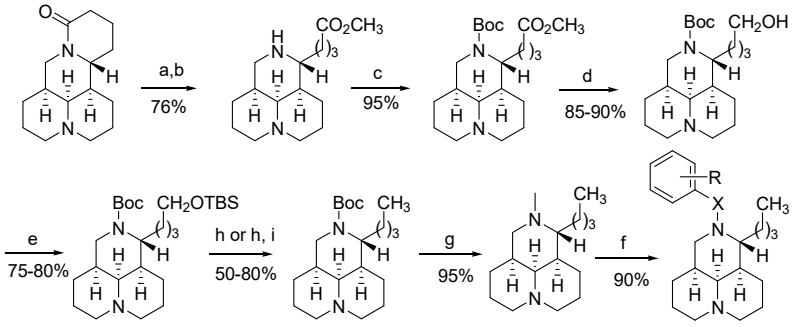
Scheme 29 Matrinic ethanol derivatives as anti-HCV agents

It is necessary to develop novel and broad-spectrum anti-flu agents in view of influenza still is a serious threat to human health and. Recently, Wang and coworkers designed and synthesized a series of 12-N-substituted tricyclic matrinic derivatives employing 12-N-*p*-cyanobenzenesulfonyl matrinane as a precursor from starting substrates sophocarpine and matrine through two pathways (Scheme 30 and 31). Their 50% cytotoxic and virus-inhibitory concentration (IC_{50} and TC_{50}) anti-influenza activities against H1N1 were investigated through the CPE inhibition assay (Scheme 32). Among these derivatives, 12*N*-Benzyl matrinane **85** showed the most crucial anti-H1N1 activity with an IC_{50} and SI value of 16.2 μM and over 33.4. Compound **85** still exhibited a significant in vivo pharmacokinetic profile and its value of an area under the curve

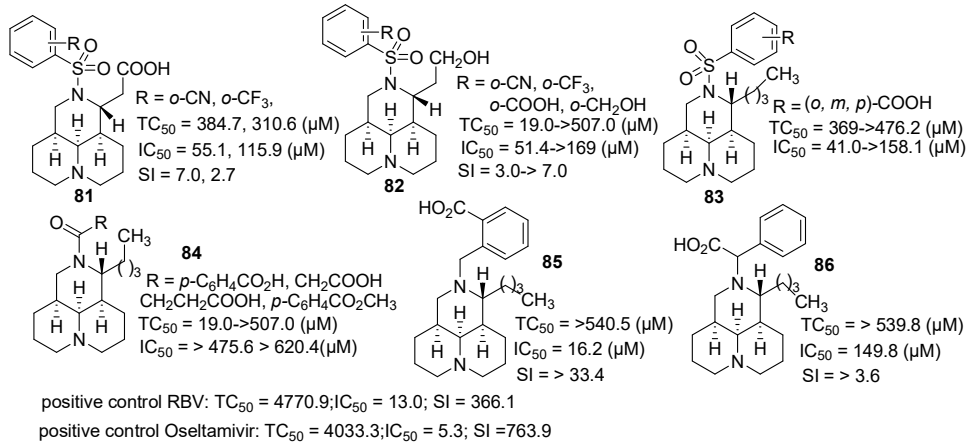
($AUC_{0-\infty}$) was 9.89 μM·h. The studies on SAR suggested that the introduction of a suitable benzyl group at the 12-*N*-position might be favorable to retain or enhance the potent activity and reduce the toxicity.



Scheme 30 Route A: a) $KMnO_4$, 10% H_2SO_4, reflux, 2 h; b) 2 N MeOH/HCl, reflux, 2 h; c) R-$C_6H_nSO_2Cl$, TEA, CH_2Cl_2, 4 h; d) 3 N HCl, reflux, 2 h; e) Boc_2O, MeOH, K_2CO_3, r.t., 4 h; f) $LiAlH_4$, THF, r.t., 30 min; g) 2 N HCl/Et_2O, r.t., 30 min; h) TBSCl, CH_2Cl_2, imidazole, r.t., overnight; i) R-$C_6H_nSO_2Cl$, TEA, CH_2Cl_2, 4 h; j) 2 N HCl, r.t., 2 h.

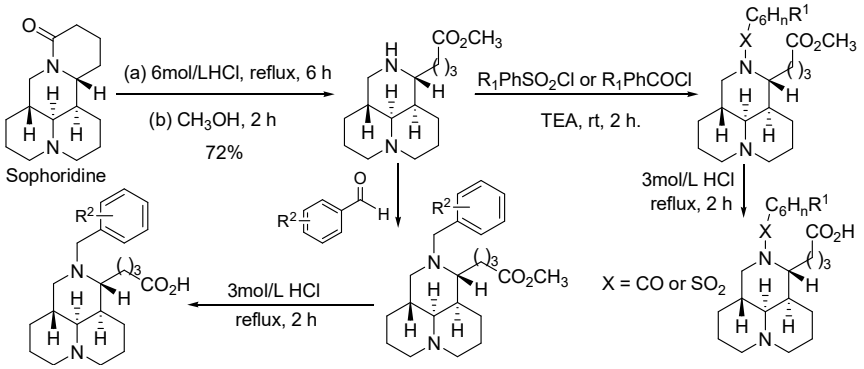


Scheme 31 Route B: a) 5 N NaOH, reflux, 9 h, 6N HCl, pH = 5–6; b) 2 N MeOH/HCl, reflux, 2 h; c) Boc_2O, CH_2Cl_2, TEA, r.t.,4 h; d) $LiAlH_4$, THF, r.t., 30 min; e) TsCl, CH_2Cl_2, TEA, 4-DMAP; f) $LiAlH_4$, THF, r.t., 30 min; g) 2 N HCl/Et_2O, 30 min; h) Benzyl bromide/Acyl chloride/sulfonyl chloride TEA, MeCN or CH_2Cl_2; i) 3 N NaOH, 2 h.

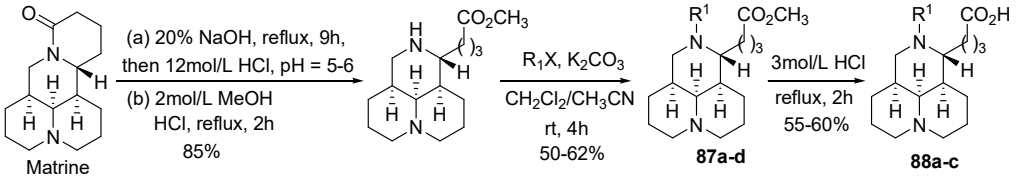


Scheme 32 12N-substituted tricyclic matrinic derivatives as anti-influenza agents

Ebola virus (EBOV) along with the marburgvirus (MARV) as a filamentous virus constitutes the filovirus family and it can cause an acute lethal hemorrhagic fever in humans. Song group [71] synthesized types of tricyclic derivatives with a common chlorinated benzene motif using sophoridine and matrine as starting substrates and assayed their anti-ebolavirus (EBOV) activities (Scheme 33 and 34). Among all these derivatives, compound 8**7d** (3',4'-$Cl_2C_6H_3CH_2$) demonstrated the most potent anti-ebolavirus activity and its IC_{50} and SI value anti-EBOV were 5.29 μmol/L and over 37.8. Compound 8**7d** also exhibited an encouraging broad-spectrum against EBOV and MARV activity in vivo. Its anti-EBOV activity (65% reduction) was significantly higher than that of positive drug sertraline (45% reduction). Preliminary studies on structure−activity relationship indicated N-dichlorobenzyl fragment at the 12 position was beneficial for the anti-filovirus activity and there was no action toward the activity of the compounds in chiral configuration at C5 atom. These results provided efficient information on further design and optimization of novel potential anti-filovirus agents.



Scheme 33 Anti-ebolavirus (EBOV) activities of sophoridine derivatives

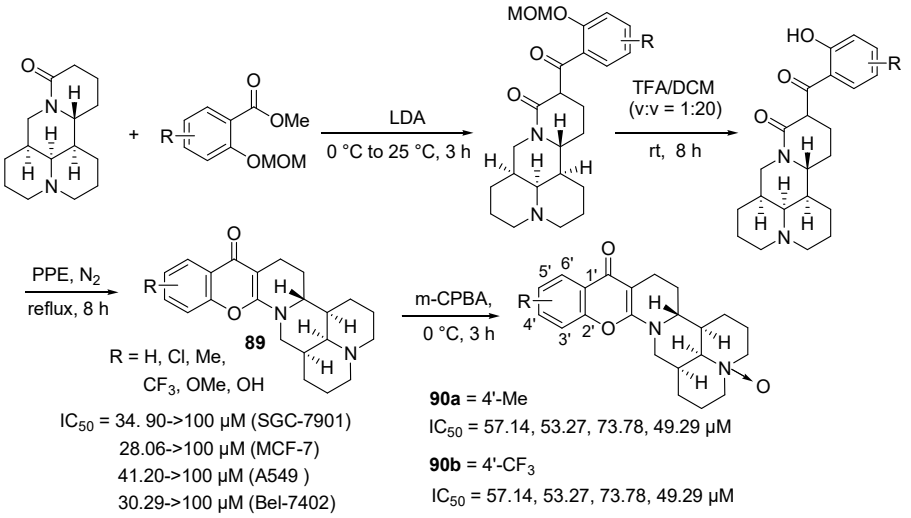


Scheme 34 Anti-ebolavirus (EBOV) activities of matrine derivatives

6. Fusing D ring and derivatization

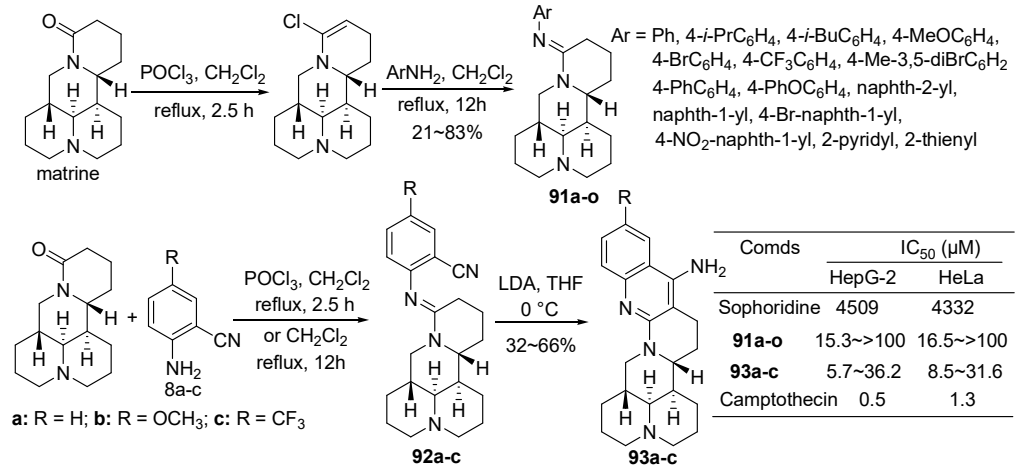
In 2016, a series of matrine derivatives of fusing D ring [72] prepared and their anti-proliferative activities against four human cancer cell lines in vitro were evaluated through MTT assay (Scheme 35). Compared with the parent matrine, most of the derivatives exhibited more potent inhibitory activities toward four human cancer cell lines SGC-7901, MCF-7, A549 and Bel-7402 (IC_{50} = 34. 90->100 μM, 28.06->100 μM, 41.20->100 μM and 30.29->100 μM). Particularly, compounds **89f** (R = 4'-Cl) showed the strongest cytotoxic activity against four cancer cells with IC_{50} value of 25.23-36.03 μM. Mechanistic studies demonstrated that the anticancer action of **89f** might mainly involve the inducing G1 cell cycle arrest and inhibiting cell migration in Bel-7402 and HepG2 cells via up-regulation of P21, P27 and E-cadherin and down-regulation of N-cadherin.

Further studies indicated that compound **89f** inhibited the proliferation of hepatocellular cancer cells in a time- and dose-dependent manner.



Scheme 35 Matrine derivatives of fused D ring as anti-hepatocellular cancer agents

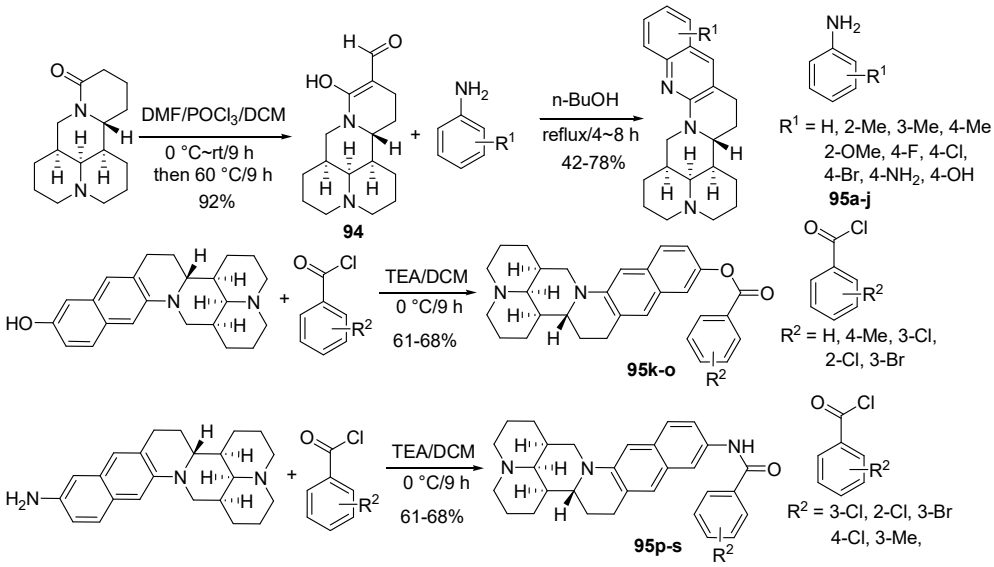
Recently, types of derivatives from sophoridine imine were synthesized and their anticancer activities in vitro based on the binding mode of camptothecin with Topo I were evaluated[73]. Compared with positive drug camptothecin, all these derivatives exhibited less potent activity against HepG-2 and HeLa cell lines. The strongest activity of compound **93b** (R = OMe) showed anti-proliferative activities toward HepG-2 and HeLa cell lines with IC_{50} values of 5.7 μM and 8.5 μM (Scheme 36). Molecular docking analysis demonstrated that the formation π-π stacking interaction with DNA Topo I through the introduction of conjugated planar structure resulting in enhancing of biological activity. The mechanism was inhibition of the activity of DNA Topo I and induction of cell cycle arrest at the G0/G1 phase to cause apoptotic cell death. The studies provided an important pathway for the development of novel Topo I inhibitor via structural optimizations active lead compounds.



Comds	IC_{50} (μM)	
	HepG-2	HeLa
Sophoridine	4509	4332
91a-o	15.3~>100	16.5~>100
93a-c	5.7~36.2	8.5~31.6
Camptothecin	0.5	1.3

Scheme 36 Sophoridinic imine derivatives as potent anticancer agents

In 2018, a series of derivatives quinolinomatrine from natural product matrine were synthesized and assayed their pesticidal activities against *Mythimna separata* and *Tetranychus cinnabarinus* (Scheme 37)[74]. Studies on SAR demonstrated that the introduction of a chlorine atom at the C-21 position of quinolinomatrine was helpful for the insecticidal and acaricidal activities (Table 4). For example, compounds **95g** (R^1 = Cl) exhibited more potent insecticidal and acaricidal activities against two crop-threatening insect pests (*Tetranychus cinnabarinus* and *Mythimna separata*) with corrected mortality rate of 37.1% after 72 h and 69.0% after 34 days, and corrected mortality rate of positive control spirodiclofen was respectively 67.5% and 48.3% at the same conditions.



Scheme 37 Pesticidal activities of a series of quinolinomatrine derivatives

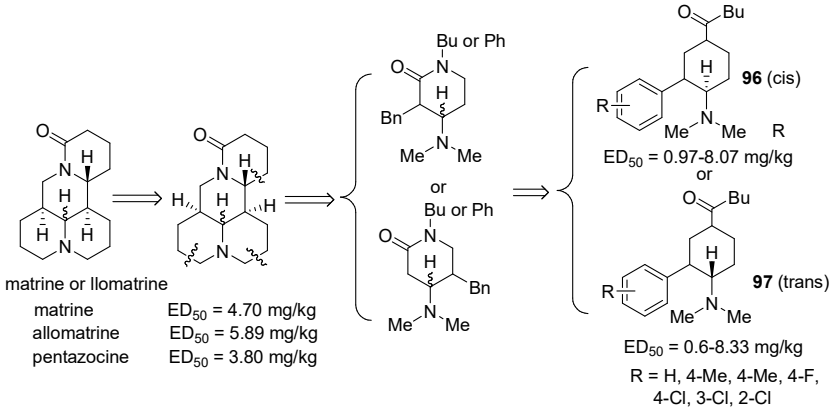
Table 4 Insecticidal activity of compounds against *T.cinnabarinus* and *M. separata*

Compd	T. cinnabarinus		*M. separata*		
	Corrected mortality rate (%)		Corrected mortality rate (%)		
	C = 0.5 mg/mL		C = 1.0 mg/mL		
	48 h	72 h	10 days	25 days	34 days
Matrine	4.8	15.7	6.7	17.3	24.2
94	5.5	19.3	10.0	24.2	31.1
95a-s	3.2~15.5	15.7~37.1	6.7-30.0	24.2-55.2	24.2-62.1
spirodiclofen	38.3	67.4	16.7	31.1	48.3

7 Structural simplification

Narcotic analgesics such as μ-opioid agonists receptor (MOR) can generate adverse effects including addiction, depression and constipation etc. Compared with conventional MOR agonists, κ-opioid receptor (KOR) agonists might availably lower the similar adverse effects as MOR agonists. Higashiyama group found matrine and its stereoisomer allomatrine demonstrated potent antinociceptive effects and are prospective to become novel KOR agonists[47,48]. In 2016, the

group obtained lead compounds with potent antinociceptive properties through the optimization of the structure matrine alkaloids. On the basis of lead compounds, types of compounds with amide and tertiary amine group were designed and synthesized and their antinociceptive effects were assayed through acetic acid writhing test in 30–40 mice (Scheme 38). Compounds **96** and **97** exhibited potent antinociceptive effects with ED_{50} value of 0.91-8.07 mg/kg and 0.60-8.33 mg/kg, and ED_{50} value of the parent matrine, allomatrine and positive drug pentazocine were 4.70 mg/kg, 5.89 mg/kg and 3.8 mg/kg, respectively. These results provided a valuable pathway for the development of novel KOR selective agonists through the simplification of structure of matrine-family alkaloids. These studies also indicated that the structural simplification of matrine-family alkaloids may be an efficient and new tactics for the development of other bioactive compounds such as antitumor, insecticidal and antiviral activities.



Scheme 38 Structural simplification of matrine-family alkaloids as κ opioid receptor agonists

8. Conclusion

Matrine-family alkaloids have attracted great interests from medicinal scientists in view of their extensive bioactivities and therapeutic properties over the past several decades. However, most of these alkaloids only display moderate pharmacological effects and limit their applications in a way. Matrine-family alkaloids possess satisfactory solubility, flexibility chemical structure and favorable safety and are regarded as ideal semi-synthetic precursors. At present, structural modifications using matrine-family alkaloids as precursor mainly focus on the changes of D ring such as derivatization of C-13, C-14 or C-15, opening and fusing D ring. These studies provided some valuable antitumor, antiviral and insecticidal derivatives and helped us to understand mechanism of highly antitumor candidates.

Although the structural modifications based on matrine-type alkaloids have obtained parts of highly potent bioactive candidates. To explore novel modificatory strategies still are very necessary and highly interesting, for example, new derivatives can be designed through the direct oxidative functionalization of Csp^3–H bond adjacent to N-atom of amide or tertiary amine and introduce functionalized group to C-2, C-10 or C-17 position in matrine-family alkaloids. Referring to the chemical structure of highly active compounds, opening A or B ring and

derivatization of the corresponding products perhaps are efficient strategies. In addition, the development of new bioactive such as immunosuppressive, neuroprotective and cardioprotective derivatives are is also quite urgent. More attention on structural modifications of matrine-type alkaloids should be paid to develop sequentially new design strategies, explore novel and highly potent bioactive derivatives and further survey their mechanism with target molecules in the future.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21562016) and the Natural Science Foundation of the Guizhou Science and Technology Department (JZ [2014]2010 and [2018]1077).

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Graphical Abstract

Matrine-Family Alkaloids: Versatile Precursors for the Bioactive Modifications

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This review mainly introduces recent advances in the bioactive modifications of matrine-family alkaloids from derivatization at the C-13, C-14, C-15 position, opening D ring and derivatization, fusing D ring and derivatization, structural simplification based on matrine-family alkaloids.