Synthesis and biological evaluation of sophocarpinic acid derivatives as anti-HCV agents

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Abstract Chronic hepatitis C virus (HCV) infection has become a major public health burden worldwide. Twenty-two sophocarpinic acid or matrine derivatives were synthesized and their anti-HCV activities were evaluated in vitro. The structure-activity analysis revealed that (i) sophocarpinic acids with a D-seco 3-ring structure scaffold were more favorable than matrines with a 4-ring scaffold; (ii) the introduction of an electron-withdrawing group on the phenyl ring in 12-N-benzenesulfonyl Δβγ sophocarpinic acids was beneficial for the antiviral activity against HCV. Among them, compounds 9h and 9j exhibited the most potent inhibitory activities on HCV replication with selectivity indices of 70.3 and 30.9, respectively. Therefore, both were selected as antiviral candidates for further investigation.

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1. Introduction

Chronic hepatitis C virus (HCV) infection has become a major public health burden worldwide. The World Health Organization (WHO) reported that over 3% of the global population with approximately 180 million individuals is estimated to be infected with HCV, with a 3–4 million new cases appearing every year globally. Among all countries, China accommodates the largest HCV-infected population, with more than 41 million people infected, and the incidence rate is rising year by year. In nearly 85% of the cases, the disease progresses into chronicity, and 30 percent of the cases may progress to liver cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC).

There is no vaccine to prevent HCV infection. The standard therapy for HCV in the clinic is the combination of pegylated-interferon with ribavirin. The regimen is only effective in approximately 40% of patients infected with HCV genotype 1, the prevalent HCV genotype in the United States, Europe, and China, and is associated with significant side effects. The introduction of Telaprevir and Boceprevir was temporarily effective with drug-resistant HCV, but drug-resistant mutations soon appeared. Sofosbuvir, a new HCV NS5B polymerase inhibitor approved by FDA in 2013 showed promise in dealing with drug-resistant HCV. However, a S282T mutation in NS5B was found in genotype 1a, 1b and 2a replicons, and caused a reduced susceptibility to sofosbuvir, again raising the need for new drugs with novel modes of action.

Matrine (1, Fig. 1), a quinolizidine natural product extracted from Sophora flavescentis, has been used clinically for HBV treatment for decades and has a novel mechanism of action. Clinical reports showed that compound 1 was also effective for HCV patients in China. Bearing a unique 4-ring core scaffold, compound 1 strongly provoked our interest to explore its anti-HCV structure-activity relationship (SAR) in an effort to discover a new chemical entity (NCE) against HCV with a novel mechanism. SAR studies have been carried out in our lab, revealing that the 5 configuration in the core scaffold is beneficial for anti-HCV activity. In the present study, the 55 configuration was maintained and further SAR analysis was directed toward the carbon-carbon double bond in sophocarpine (2, Fig. 1), another natural product extracted from Sophora flavescentis. Based on this strategy, a series of (E)-Δβγ/Δαβ-sophocarpinic acid (3/4, Fig. 1) derivatives bearing a D-seco 3-ring scaffold were synthesized and evaluated for their anti-HCV activities.

2. Results and discussion

2.1. Chemistry

As showed in Scheme 1, compound 2, as the starting material, was hydrolyzed in strong base and formed an isomeric mixture of 3 and 4. The target compounds (E)-12-N-substituted-Δβγ/Δαβ-sophocarpinic acids (9/10) were acquired by using a three-step sequence including carboxyl protection with diphenyldiazomethane as the protective agent, 12-N-alkylation or acylation in the presence of potassium carbonate, and deprotection in m-cresol, with overall yields of 5%–12%. The regio-isomers were separated before alkylation or acylation.

To gain sophocarpinic acid derivatives without the double bond, 2 was refluxed in aqueous base as illustrated in Scheme 2 to gain the key intermediate 11, which was hydrolyzed in strong base to form a 3-ring scaffold product 12, followed by a three-step sequence including carboxyl protection via diphenyldiazomethane, 12-N-alkylation in the presence of potassium carbonate and deprotection in m-cresol to gain the desired product 15 in an overall yield of 16.1%. Matrine derivatives 16a-d (Table 1) as a class of anti-HBV agents were prepared as previously reported.

2.2. SAR analysis for anti-HCV activity in vitro

All the synthesized compounds were tested for their anti-HCV activity and cytotoxicity in Huh7.5 cells using specific real-time RT-PCR assay, as described in our previous publication. Anti-HCV activity was evaluated by measuring both EC50 (for anti-HCV activity) and TC50 (for cytotoxicity) values. As a key indication, the selectivity index (SI) was calculated as a ratio of TC50 to EC50. Anti-HCV activity of a given compound was estimated by combining its EC50 value with its SI. Twenty-two sophoridinic acid or sophoridine analogs and their anti-HCV effectiveness are shown in Tables 1 and 2.

The SAR study for anti-HCV activity was initially focused on the influence of the substitutions on ring D while the 4-ring scaffold was unchanged. As indicated in Table 1, matrine compounds 16a-c afforded similar or lower SI values compared to compound 1, while compound 16d bearing a methylamino showed a higher SI value, which hinted that suitable substitutions on ring D could enhance the activity against HCV.

Table 2 disclosed the SAR analysis on the D-meso 3-ring scaffold derivatives. The compounds bearing a carbon-carbon double bond...
double bond on the side chain, specifically, (E)-12-N-substituted-Δβγ-sophocarpinic acids (9a–k) and their isomers (E)-12-N-substituted -Δαβ-sophocarpinic acids (10a–f), were evaluated in this study. First, the influence of the substituents on the 12-nitrogen atom in the (E)-Δβγ-sophocarpinic acids was examined. The results showed that 12-N-benzyl derivatives 9a–c showed anti-HCV activities similar to or lower than compound 1, and most of the compounds in the 12-N-benzensulfonyl series (9d–k) had low activities against HCV, except that compound 9h and 9j showed significantly higher activity than compound 1 with SI values of 70.3 and 30.9, respectively. The results suggested that the introduction of CF3 or CN on the sulfonylphenyl ring might be beneficial for the anti-HCV activity.

In the case of the (E)-Δαβ-sophocarpinic acids derivatives 10a–f, most showed decreased or similar anti-HCV activities as compared to compound 1, regardless of the electron-donating or electron-withdrawing groups on the phenyl ring, which hinted that a Δβγ analog could do better than its Δαβ isomer in anti-HCV area. The introduction of OH at the double bond could decrease anti-HCV activity, as compared with product 15 and compound 9b.

All together, it appeared that a D-meso 3-ring structure scaffold was more favorable than a 4-ring scaffold, and the introduction of
an electron-withdrawing group on the phenyl ring in 12-N-
benzenesulfonyl Δβγ-sophocarpinic acid derivatives was beneficial for anti-HCV activity.

### 3. Conclusions

In searching for novel anti-HCV agents, 22 sophocarpinic acid or matrine derivatives were synthesized and evaluated for their anti-HCV activities in vitro with 1 as the lead. Among these derivatives, compounds 9h and 9j exhibited the most potent antiviral activities against HCV with SI values of 70.3 and 30.9, respectively. SAR revealed that (i) sophocarpinic acids with a D-seco 3-ring structure scaffold are more favorable than matrines with a 4-ring scaffold; (ii) introduction of an electron-withdrawing group on the phenyl ring in 12-N-benzenesulfonyl substituted Δβγ-sophocarpinic acid derivatives is beneficial for activity. In addition, compounds 9h and 9j showed satisfactory activity against coxsackievirus type B3 (CVB3) and CVB6 in our earlier study, plus good pharmacokinetic profiles with low toxicity in vivo. All together, 9h and 9j are highly recommended to be further developed as broad-spectrum antiviral drug candidates.

### 4. Experimental

#### 4.1. Chemistry

Melting point (mp) was obtained with an MPA 100 OptiMelt automated melting point system (Stanford Research Systems, California, USA) and uncorrected.

#### 1H NMR spectra was

### Table 1 SAR for anti-HCV activity of matrine analogues.

| No | R1  | R2  | TC50 (µg/mL) a | EC50 (µg/mL)b | SIc |
|----|-----|-----|----------------|----------------|-----|
| 1  | H   | H   | >1000          | 98.04          | >10.2 |
| 16a| OCH3| CH3 | >1000          | 104.62         | >9.6 |
| 16b| OCH3| CH3 | 49.87          | 5.60           | 8.9  |
| 16c| OH  | OCOCl| 54.90          | >37.04         | <1.5 |
| 16d| H   | NHCH3| 543.70         | 31.07          | 17.5 |
| RBV|     |     | 2000           | 292.46         | 6.84 |

*aCytotoxic concentration required to inhibit Vero cell growth by 50%.

*bConcentration required to inhibit CVB3 growth by 50%.

*cSelectivity index values equaled to TC50/EC50.

### Table 2 SAR for anti-HCV activity of sophocarpinic acid derivatives.

| Compd. | R                | TC50 (µg/mL) a | EC50 (µg/mL)b | SIc |
|--------|------------------|----------------|----------------|-----|
| 1      |                  | >1000          | 98.04          | >10.2 |
| 9a     | -CH3PhCH3-ο      | 726.98         | 155.66         | 4.7  |
| 9b     | -CH3Ph           | >1000          | 49.3           | 20.3 |
| 9c     | -CH3PhBr- p      | 357.41         | 24.36          | 14.7 |
| 9d     | -SO2PhNO2- p     | 380.7          | 74.0           | 5.14 |
| 9e     | -SO2Ph           | >1000          | 257.55         | >3.9 |
| 9f     | -SO2PhCH3- p     | >1000          | 112.06         | >8.9 |
| 9g     | -SO2PhOCH3- p    | >1000          | 165.21         | >6.1 |
| 9h     | -SO2PhCF3- p     | 530.07         | 7.54           | 70.3 |
| 9i     | -SO2PhCl-ο       | 876.08         | 134.58         | 6.5  |
| 9j     | -SO2PhCN- m      | 123.08         | 3.98           | 30.9 |
| 9k     | -SO2Ph(NHCOCH3)-p| 65.77          | 2.80           | 23.5 |
| 10a    | -CH3PhNO2- p     | >1000          | 52.82          | >18.9 |
| 10b    | -SO2Ph           | >1000          | 59.65          | >16.8 |
| 10c    | -SO2PhCH3- p     | 171.29         | 25.02          | 6.8  |
| 10d    | -SO2PhCl-ο       | 404.64         | 241.27         | 1.68 |
| 10e    | -SO2Ph(NHCOCH3)-p| 552.03         | 222.06         | 2.5  |
| 10f    | -SO2PhOCH3- p    | 700.4          | 291.8          | 2.4  |
| 15     | -CH3Ph           | >1000          | >333.3         | 3    |
| RBV    |                  | 2000           | 292.46         | 6.84 |

*aCytotoxic concentration required to inhibit Vero cell growth by 50%.

*bConcentration required to inhibit CVB3 growth by 50%.

*cSelectivity Index values equaled to TC50/EC50.
performed on a Varian Inova 400 MHz spectrometer (Varian, San Francisco, CA) or 500 MHz spectrometer (AV500-III, Bruker, Swiss), with Me$_4$Si as internal standard. ESI high-resolution mass spectra (HRMS) were recorded on an AutospecUltima-TOF mass spectrometer (Micromass UK Ltd., Manchester, UK). Flash chromatography was performed on CombiflashRf 200 (Teledyne, Nebraska, USA), particle size 0.038 mm.

Compound 2 with purity over 98.5% was purchased from the Yanchi Dushun Biological and Chemical Co., Ltd. (Shanxi, China) and the Ningxia Zijinghua Pharmacy Co., Ltd. (Ningxia, China). Target compounds 9b-c, 9e-k and 10b-f were prepared as a family of anti-CVIB3 inhibitors.

4.1.1. General procedures for 9 and 10

Compound 2 (12.3 g, 50 mmol, 1 equiv.) was added to a solution of KOH (33.6 g, 600 mmol) in H$_2$O (300 mL). The reaction mixture was heated and refluxed for 7 h and then stirred at room temperature overnight. The reaction solution was cooled with an ice-water bath and was acidified with HCl (3 mol/L) to pH 5–6. The solvent was removed in vacuo, and the residue was recrystallized in methanol to give an isomer mixture of 3 and 4.

A mixture of diphenylmethane hydrozone (14.7 g, 75 mmol, 1.5 equiv.) and electrolytic manganese dioxide (13.04 g, 3 equiv.) in petroleum ether (boiling range 30–60 °C) was heated at reflux for 0.5 h, and the mixture was filtered. The filtrate was added to the solution of 3 and 4 in methanol, and the mixture was then stirred overnight at room temperature. A corresponding isomer mixture of 5 and 6 was obtained and was used directly in the next reaction without further purification.

Anhydrous K$_2$CO$_3$ (3.5 equiv.) and benzyl bromide, or sulfonyl chloride (1 equiv.) were added to the solution of 5 and 6 in dichloromethane or MeCN (50 mL), and the reaction solution was then stirred at room temperature until TLC analysis showed completion of the reaction. The reaction mixture was filtered and the filtrate was evaporated to afford a mixture of 7 and 8, which were obtained by splitting of the mixture with flash column chromatography on silica gel with ethyl acetate and cyclohexane as the eluents. Compound 7 was then dissolved in m-cresol (10 mL), and the reaction mixture was stirred at 80 °C for 8–9 h. It was then cooled, and methylisobutylketone (30 mL) was added. The resulting solution was extracted with H$_2$O (50 mL x 3), and the combined extracts were evaporated to afford the crude compound, which was purified by flash column chromatography on silica gel with dichloromethane and methanol as the eluents, to afford 9. Compound 10 was obtained from compound 8 by the same method.

(E)-12-N-(p-Nitrobenzyl)-Δ$^6$-sophorpinic acid (9a): white solid (0.6 g, 6.5%), mp 98–100 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 7.13–7.31 (m, 4H), 5.95–6.06 (m, 1H), 5.30 (dd, 1H, $J=9.2$, 15.2 Hz), 4.46 (m, 1H), 3.03–3.10 (m, 3H), 2.99 (dd, 1H, $J=7.2$, 7.2 Hz), 2.82–2.93 (m, 2H), 2.42–2.61 (m, 3H), 2.31–2.33 (m, 3H), 2.19 (s, 1H), 1.87–2.03 (m, 3H), 1.41–1.79 (m, 7H); HRMS: calcd. for C$_{21}$H$_{23}$N$_2$O$_7$ (M+H)$^+$ 403.1742, found 403.1742.

(E)-12-N-(p-Methylbenzyl)-Δ$^6$-sophorpinic acid (9d): white solid (2.2 g, 9.8%), mp 176–179 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 8.36 (d, 2H, $J=8.8$ Hz), 7.99 (d, 2H, $J=8.8$ Hz), 5.44–5.47 (m, 2H), 3.76 (dd, 1H, $J=5.0$, 11.2 Hz), 3.42–3.55 (m, 1H), 3.29–3.37 (m, 1H), 3.07–3.15 (m, 1H), 2.93 (dd, 2H, $J=5.0$, 7.2 Hz), 2.79 (d, 1H, $J=11.2$ Hz), 2.68–2.69 (m, 1H), 2.50–2.54 (m, 1H), 1.90–2.11 (m, 3H), 1.30–1.83 (m, 8H); HRMS: calcd. for C$_{21}$H$_{23}$N$_2$O$_7$S (M+H)$^+$ 450.1693, found 450.1710.

(E)-12-N-(p-Nitrobenzyl)-Δ$^6$-sophorpinic acid (10a): white solid (0.95 g, 9.5%), mp 139–141 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 8.12–8.15 (m, 2H), 7.51–7.57 (m, 2H), 6.97–7.04 (m, 1H), 5.85 (d, 1H, $J=15.0$ Hz), 4.23 (d, 1H, $J=14.8$, 3.27–3.47 (m, 4H), 2.90–3.01 (m, 3H), 2.79–2.85 (m, 1H), 2.47–2.78 (m, 3H), 2.19–2.22 (m, 1H), 1.93–2.08 (m, 2H), 1.65–1.88 (m, 7H); HRMS: calcd. for C$_{23}$H$_{33}$N$_2$O$_4$ (M+H)$^+$ 400.2236, found 400.2217.

4.1.2. Procedures for 12-N-benzyl-β-hydroxyl sophorpinic acid (15)

To a solution of KOH (33.6 g, 0.6 mol) in water (600 mL) was added 2 (12.3 g, 0.05 mol) with stirring at room temperature. The reaction mixture was refluxed for 8 h, then cooled down to 0 °C and neutralized with 3 mol/L HCl. After concentrated in vacuo, MeOH (150 mL) was added, insoluble solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel using CH$_2$Cl$_2$/MeOH as eluent to give 11 (6.2 g, 47%) as white solid.

Compound 11 (1 equiv.) was added to a solution of KOH (10%) in water. The reaction mixture was refluxed for 9 h, and then stirred at room temperature overnight. The reaction solution was cooled in ice-water bath, and acidified with HCl (3 mol/L). The solvent was removed in vacuo and the residue was dissolved in methanol to give a corresponding solution of crude 12.

A mixture of diphenylmethane hydrozone (14.7 g, 75 mmol, 1.5 equiv.) and electrolytic manganese dioxide (13.04 g, 150 mmol, 3 equiv.) in petroleum ether (boiling range 30–60 °C) was heated at reflux for 0.5 h, and the mixture was filtered. The filtrate was added to the solution of 13 in methanol, and the mixture was then stirred at room temperature until the purple color disappeared, and then filtered. The resulting filtrate was evaporated under reduced pressure to dryness. The residue was washed with petroleum ether to afford crude compound 13 which was used directly in the next step without further purification.

To the mixture of crude 13 and anhydrous K$_2$CO$_3$ (3 equiv.) in MeCN was added benzyl bromide (1 equiv.). The reaction mixture was stirred at room temperature till the reaction was complete (checked by TLC), then filtered. The filtrate was evaporated in vacuo to give the crude product 14 as an oily residue, which was then dissolved in m-cresol (10 mL), and the reaction mixture was stirred at 80 °C for 8–9 h. It was then cooled, and methylisobutylketone (30 mL) was added. The resulting solution was extracted with H$_2$O (50 mL x 3), and the combined extracts were evaporated to dryness, and the residue was purified through flash chromatography over silica gel to give 1.5 g of compound 15. White solid (1.5 g, 16.1%), mp 115–117 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 7.26–7.44 (m, 5H), 4.38–4.47 (m, 1H), 4.08–4.13 (m, 1H), 3.72–3.74 (m, 1H), 3.15–3.25 (m, 2H), 2.76–3.18 (m, 3H), 2.59–2.70 (m, 1H), 2.32–2.49 (m, 3H), 1.85–2.25 (m, 6H), 1.39–1.72 (m, 7H); HRMS: calcd. for C$_{23}$H$_{33}$N$_2$O$_4$ (M+H)$^+$ 373.2491, found 373.2493.

4.2. Biological methods

4.2.1. Cell culture

Human liver cell line Huh7.5 cells (kindly provided by Vertex Pharmaceuticals, Inc., Boston, MA) were cultured in Dulbecco’s modified eagle medium (DMEM) supplemented with 10%
HCV RNA was quantified with 1 mmol/L protease inhibitor cocktail. The intracellular plates were extracted with Cyto-Buster Protein Extraction Reagent (Qiagen), and total intracellular proteins (in 6-well plates) were extracted with RNeasy Mini Kit (Qiagen), and total intracellular RNA (in 96-well plates) was extracted with the test compounds at various concentrations or solvent control. The culture medium was removed after 72 h inoculation, treated with the test compounds at various concentrations or solvent inactivated fetal bovine serum and 1% penicillin–streptomycin (Invitrogen). Cells were digested with 0.05% trypsin–ethylene diamine tetraacetic acid (EDTA) and split twice a week.

4.2.2. Anti-HCV effect in vitro
Huh7.5 cells were seeded into 96-well or 6-well plates (Costar) at a density of 3 × 10^4 cells/cm². After 24 h incubation, the cells were infected with HCV viral stock (45 IU/cell) and simultaneously treated with the test compounds at various concentrations or solvent as control. The culture medium was removed after 72 h inoculation, and total intracellular RNA was extracted with Cyto-Buster Protein Extraction Reagent added with 1 mmol/L protease inhibitor cocktail. The intracellular HCV RNA was quantified with a real-time one-step reverse-transcription polymerase chain reaction (RT-PCR).

4.2.3. Cytotoxicity assay
Huh7.5 cells were seeded into 96-well plates (Costar) at a density of 3 × 10^4 cells/cm². After incubated for 24 h, fresh culture medium containing test compounds at various concentrations were added. Seventy-two hours later, cytotoxicity was evaluated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT).

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