Chinese Chemical Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis and biological evaluation of 12-benzyl matrinic amide derivatives as a novel family of anti-HCV agents

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ARTICLE INFO

Article history:
Received 30 November 2015
Received in revised form 4 February 2016
Accepted 4 March 2016
Available online xxx

Keywords:
Matrinic acid
Matrinic amide
Hepatitis C virus
Structure–activity relationship

ABSTRACT

A new series of 12-benzyl matrinic amide/ethanamide derivatives were synthesized from matrinine (**1**) and evaluated for their anti-HCV activity, taking compound **2** as the lead. SAR revealed that the introduction of a suitable substituent at the *N*′-end of matrinic amide might greatly enhance the potency. Among them, matrinic acid **17** and *N*′-substituted matrinic amides **18a**–**d** exhibited promising potency with low micromolar EC_{50} values ranging from 1.03 μmol/L to 7.54 μmol/L, and better therapeutic window with SI from 66 to 132. Moreover, compound **17** displayed an excellent PK and safety profile *in vivo*, demonstrating good drug-like characteristics. Thus, it has been selected for further investigation, with an advantage of decreased chances of inducing drug-resistance mutations.

1. Introduction

Currently, hepatitis C virus (HCV) infection has become a major public health problem and heavy burden worldwide [1–3]. Recently, the direct-acting antivirals (DAAs), which specifically target HCV proteins had made great progresses. Telaprevir and Boceprevir in combination with peg IFN-α plus RBV, as the first generation of NS3/4A HCV protease inhibitors, have been widely used in clinic for the treatment of HCV infections. However the side effects, drug interactions and resistance mutations have limited their clinical use [4–7]. Several new HCV DAAs and their combinations have been approved since the end of 2013, such as NS3/4A inhibitors Simeprevir and Asunaprevir, NS5A inhibitors Ledipasvir and Daclatasvir and NS5B polymerase inhibitors Sofosbuvir and Dasabuvir [8]. Especially, some new HCV DAAs and their triple therapies show significant promise in some drug-resistant HCV in clinical patients. However, their chemotherapeutic pressure is on viral components; thus, antiviral therapies targeting specific viral enzyme might cause drug-resistant mutations [9]. Therefore, novel antiviral therapeutic strategies against HCV with no or decreased chance of inducing drug-resistance are highly desirable [10].

We have successfully identified 12-benzyl matrinic acid analogs to be a novel class of anti-HCV agents from matrine (**1**, Fig. 1), a Chinese natural product [11]. The representative compound, 12-*p*-methoxylbenzyl matrinic acid (**2**, Fig), demonstrated a moderate activity with EC_{50} of 118 μmol/L and SI of over 22 [12–14]. Its mode of action is down-regulating host heat-stress cognate 70 (Hsc70) protein expression at the post transcriptional level through destabilizing Hsc70 mRNA, a distinctly different action mode from the currently used drugs such as Telaprevir and Simeprevir [12]. As the target is not on the viral component, this kind of antiviral agents might inhibit viral replication with decreased chance of causing drug-resistant mutations [14].

This unique action mode and special scaffold of compound **2** strongly provoked our interest to continuously explore the structure–activity relationship (SAR) of this kind of compounds, in an effort to discover novel anti-HCV candidates with an advantage of overcoming the drug resistance. Therefore, in the present study, taking compound **2** as the lead, SAR studies were further conducted with the variations of the 4′-carboxyl group and the shortening length of the 11-side chain. Based on this strategy, a series of new 12-benzyl matrinic amide/ethanamide and matrinic acid/amine derivatives were constructed and evaluated for their *in vitro* anti-HCV activity as well as the *in vivo* pharmacokinetic (PK) and safety profile of the representative compounds.

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http://dx.doi.org/10.1016/j.cclet.2016.03.006

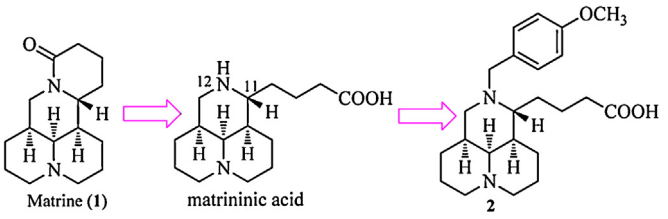

Fig. 1. Chemical structures of matrinine (**1**), matrinic acid and 12-*p*-methoxylbenzyl matrinic acid (**2**).

2. Experimental

2.1. Chemistry

Melting points (mp) were obtained using a CXM-300 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer or Bruker Avance III 500 spectrometer (Varian, San Francisco, CA) respectively, in $CDCl_3$, DMSO or CD_3OD using Me_4Si as the internal standard. Flash chromatography was performed on Combiflash Rf 200 (Teledyne, Nebraska, USA). All the target compounds were synthesized using commercially available sophocarpine (**3**) and matrine (**1**) with purity over 98% as the starting material, which were purchased from the Yanchi Dushun Biological and Chemical Co., Ltd. (Shanxi, China).

2.1.1. General procedures for methyl N-substituted matrinic acetate (*16a–b*)

Matrine (**1**, 1.0 g, 4 mmol) was added to 5 mol/L NaOH (20 mL), and the reaction mixture was heated under reflux for 9 h, cooled in an ice bath and then acidified with HCl (6 mol/L) to pH 4–5. The solvent was removed under reduced pressure, and the residue was dissolved in methanol (100 mL). The suspension was filtered and the filtrate was concentrated. The residue was dissolved in 2 mol/L HCl/MeOH (20 mL) and the mixture was refluxed for 2 h. The crude compound **15** was obtained by evaporation and used in the next step without further purification. Anhydrous K_2CO_3 (3.5 equiv.) and benzyl bromide (1.5 equiv.) were added to a solution of compound **15** (1.0 equiv.) in MeCN (20 mL), and the reaction solution was stirred at room temperature until TLC analysis showed completion of the reaction. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed by water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated to afford crude compounds **16a–b**. The title compounds **16a–b** were obtained by purifying with flash column chromatography on silica gel with dichloromethane and methanol as the eluents in yields of 50%–60%.

2.1.2. 12-(4-Pyridylmethyl) matrinic acid dihydrochloride (*17*)

Compound **16b** (1.5 mmol) was refluxed in 3 mol/L HCl (15 mL) for 1 h, then cooled, and adjusted to pH 5–6 with 3 mol/L KOH. The solution was extracted with ethyl acetate, and the aqueous layer was evaporated to dryness, and the residue was purified through flash chromatography over silica gel to give the title compounds **17**. White solid yield: 83%, mp: 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (s, 1H), 12.01 (s, 1H), 11.08 (s, 1H), 8.68 (d, 2H, J = 6.0), 7.73 (d, 2H, J = 6.0), 5.02 (s, 1H), 4.22 (s, 1H), 4.05–3.95 (m, 2H), 3.58 (s, 1H), 3.24 (t, 2H, J = 14.0), 2.84–2.96 (m, 2H), 2.78 (s, 1H), 2.65 (s, 1H), 2.50 (s, 1H), 2.34 (s, 2H), 1.51–2.07 (m, 12H); ^{13}C NMR (101 MHz DMSO-d_6): δ 174.3, 149.5 (2), 139.4, 126.0 (2), 60.7, 60.2, 56.0, 54.2 (2), 49.1, 35.9, 32.8, 29.9, 27.9, 23.9, 23.5, 21.6, 17.9 (2); HRMS: calcd. for $C_{21}H_{32}N_3O_2{\cdot}2HCl$ $[M-2HCl+H]^+$: 358.2495, found: 358.2482.

General procedures for other title compounds and their physical and spectroscopic characterization data were given in Supporting information.

2.2. Biological methods

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% 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.

2.2.1. Anti-HCV effect in vitro [15]

Huh7.5 cells were seeded into 96-well or 6-well plates (Costar) at a density of 3.0×10^4 cells/cm^2. After 24 h of incubation, the cells were infected with HCV viral stock (recombination virus strain J6/JFH/JC, 45 IU/cell) and simultaneously treated with the test compounds at various concentrations. The culture medium was removed after 72 h of incubation, and the intracellular total RNA (in 96-well plates) was extracted with RNeasy Mini Kit (Qiagen), and total intracellular proteins (in 6-well plates) were 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).

2.2.2. Cytotoxicity assay [15]

Huh7.5 cells were seeded into 96-well plates (Costar) at a density of 3.0×10^4 cells/cm^2. After 24 h of incubation, fresh culture medium containing test compounds at various concentrations were added. 72 h later, cytotoxicity was evaluated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT).

2.2.3. Pharmacokinetic studies

Animals were purchased from the Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences, Beijing, China. All experimental procedures were approved by the Biomedical Ethics Committee of the Chinese Academy of Medical Sciences for Animal Use and Protection. Three male SD rats with weights in the range of 180–220 g were used in each study. Each rat was administered orally with compounds at a dose of 25 mg/kg. Blood samples (0.3 mL) were collected at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 4.0, and 6.0 h and were immediately centrifuged to separate the plasma fraction. The plasma samples obtained were stored at −20 °C until analysis. Concentration–time profile was obtained for each analyte, and standard noncompartmental analysis was performed on the data using WinNonlin, Version 5.3 to determine the AUC and other noncompartmental parameters.

3. Results and discussion

As depicted in Scheme 1, the matrinic acetic acid **7** was obtained from compound **3** using a four-step sequence including oxidation, esterification, 12-substitution and ester hydrolysis with overall yields of 30%–35%. The desired matrinic ethanamides (**8a–b**) were prepared using **7** and NH_4HCO_3 *via* the mixed anhydride procedures in 70%–80% yields [16]. *N*′-Substituted matrinic ethanamides (**9a–c**) were obtained by the coupling of **7** with different amines [17] with good yields of 65%–70%.

As shown in Scheme 2, the matrinic amide products **14a–e** were acquired from compound **1** using a five-step sequence including ring-opening, 12-protection *using tert*-butoxycarbonyl (Boc), amidation of carboxyl, de-protection of Boc and 12-substitution with 30%–40% overall yields. The key intermediates (**16a–b**) were gained from **1** in ideal yields as described

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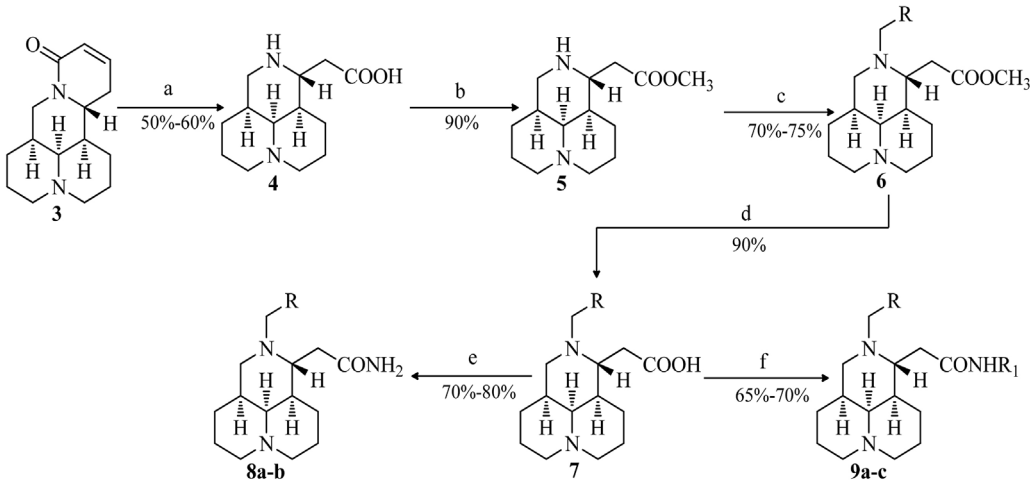
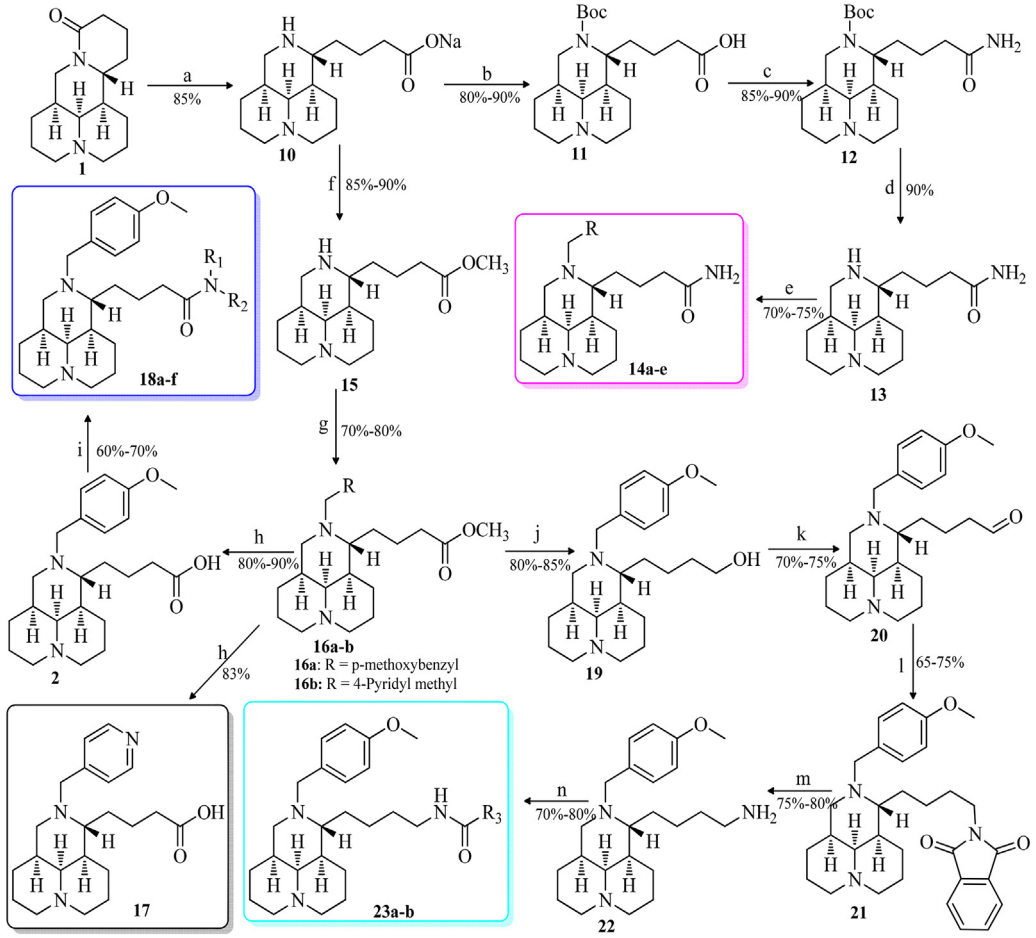


Scheme 1. Synthetic route of matrinic ethanamide derivatives. (a) 10% H_2SO_4, $KMnO_4$, reflux, 2 h; (b) 2 N MeOH/HCl, reflux, 2 h; (c) RCH_2Br, K_2CO_3, MeCN, r.t., 8 h; (d) 3 mol/L HCl, reflux, 1 h; (e) Boc_2O, NH_4HCO_3, pyridine, MeCN, r.t., 8 h; (f) EDCI, HOBt, TEA, NH_2R_1, CH_2Cl_2, r.t. 4 h.



Scheme 2. Synthetic route of matrinic acid/amide and *N*′-acyl matrinic amine derivatives. (a) 5 mol/L NaOH, reflux, 9 h; (b) Boc_2O, MeOH, r.t., 4 h, 10% citric acid, pH 4–5; (c) Boc_2O, NH_4HCO_3, pyridine, MeCN, r.t., 8 h; (d) 2 mol/L HCl/Et_2O, 30 min; (e) RCH_2Br, K_2CO_3, MeCN, r.t., 8 h; (f) 2 mol/L MeOH/HCl, reflux, 2 h; (g) RCH_2Br, K_2CO_3, MeCN, r.t., 8 h; (h) 3 mol/L HCl, reflux, 1 h; (i) EDCI, HOBt, TEA, NHR_1R_2, CH_2Cl_2, r.t. 8 h; or 2 mol/L HCl/Et_2O, 30 min; (j) $LiAlH_4$, THF, r.t., 30 min; (k) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −78 °C, 30 min; (l) *o*-phthalimide, $ClCH_2CH_2Cl$, reflux, 4 h, STAB, r.t., overnight; (m) hydrazine hydrate, EtOH; (n) EDCI, HOBt, TEA, NHR_1R_2, CH_2Cl_2, r.t. 8 h; or 2 mol/L HCl/Et_2O, 30 min.

previously [12,18]. The desired product **17** was obtained by the hydrolysis of compound **16b** in 83% yield. The products **18a–e** were synthesized from compound **2** using standard coupling protocols with yields of 60%–70%, and **18f** was produced after the removal of *N*-Boc of **18d** in high yield. The target compounds **23a–b** were generated *via* a five-step procedure, including ester reduction by $LiAlH_4$, selective oxidization of hydroxy group, reductive amination using sodium triacetoxyborohydride [19] (STAB), hydrazinolysis and amino-acylation from **16a** with overall yields of 20%–30%. All the final products were purified by flash column chromatography on silica gel with CH_2Cl_2/CH_3OH as gradient eluents.

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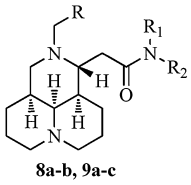
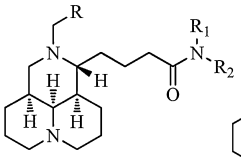
All the newly synthesized compounds were examined for their anti-HCV activity (EC_{50}) and cytotoxicity (TC_{50}) in human Huh7.5 cells using the specific real-time RT-PCR assay. As an important indicator, the selectivity index (SI) was calculated as a ratio of TC_{50} to EC_{50}. Anti-HCV ability of each compound was estimated by combining its EC_{50} and SI values. Nineteen matrinic amide/ethanamide and acid/amine derivatives and their anti-HCV effects are shown in Table 1.

First, the *p*-methoxylphenyl on the nitrogen-12 atom was replaced with a *p*-pyridyl. The resultant compound **17** exerted an activity with EC_{50} of 7.54 μmol/L and SI of over 66 (Table 1), better than those of **2**. Second, 12-pyridylmethylene and 12-methoxylbenzyl were retained, and SAR investigation was focused on the influence of 4′-carboxyl and shortening length of the 11-side chain, with which a series of new matrinic amide (**14a–e**) and matrinic ethanamide (**8a–b**) derivatives were constructed and measured. As described in Table 1, compounds **8a**, **14a** and **14d–e** displayed a reasonable activity with EC_{50} ranging from 9.6 μmol/L to 97.8 μmol/L and SI from 10 to over 29. These data suggested that replacing carboxyl with amido group might not greatly improve the potency against HCV, regardless of the length of the 11-side chain.

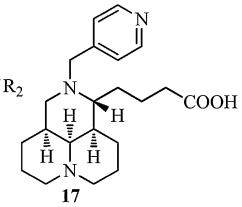
Table 1
SAR of matrinic derivatives for anti-HCV activity.



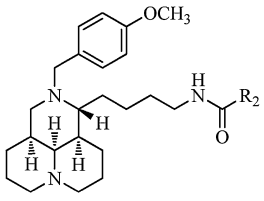
8a-b, 9a-c



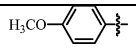
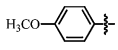
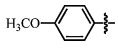
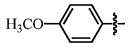
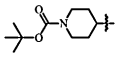
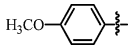
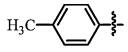
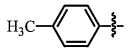
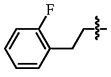
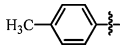
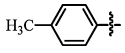
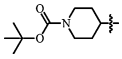
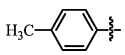
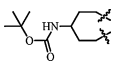
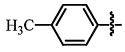
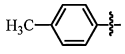
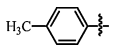
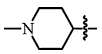
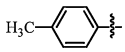
14a-e, 18a-f



17



23a-b

Compd.	R	R_1	R_2	CC_{50} (μmol/L)	EC_{50} (μmol/L)	SI[a]
8a		H	H	>500	17.0 ± 0.86	>29
8b		H	H	>500	97.8 ± 47.6	>5.1
9a		H		27.8 ± 2.19	5.09 ± 1.56	5.0
9b		H		16.3 ± 0.96	2.18 ± 1.69	7.0
9c		H		42.7 ± 0.39	2.12 ± 2.02	20
14a		H	H	>500	52.2 ± 7.08	>10
14b		H	H	>500	150.3 ± 2.45	>3.2
14c		H	H	>500	90.9 ± 37.1	>5.5
14d		H	H	>500	24.0 ± 2.32	>21
14e		H	H	240.2 ± 86.2	9.59 ± 2.56	25
17				>500	7.54 ± 2.20	>66
18a		H		161.0 ± 12.9	1.22 ± 0.32	132
18b		H		492.2 ± 7.00	4.89 ± 3.15	101
18c		H		222.7 ± 11.8	2.76 ± 0.64	81
18d				98.3 ± 8.99	1.03 ± 0.22	96
18e				>500	14.1 ± 3.37	>35
18f				58.4 ± 11.6	5.26 ± 0.39	11
23a				116.0 ± 5.31	14.4 ± 5.49	8.0
23b				112.1 ± 14.7	5.00 ± 0.42	22
Telaprevir				47.6 ± 0.61	0.02 ± 0.016	1950

[a] Selectivity index (SI) value equaled to CC_{50}/EC_{50}.

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Table 2
PK parameters[a] of the key compounds in rats after single oral dosing ($n = 3$).

Compd	T_{max} (h)	C_{max} (μmol/L)	AUC_{0-t} (μmol/L h)	$AUC_{0-\infty}$ (μmol/L h)	MRT (h)	$t_{1/2}$ (h)
14a	0.75	1.47	4.89	–	2.77	–
17	1.17	3.97	16.69	16.71	2.94	2.70
18a	0.25	0.11	0.21	0.23	2.75	4.43
18b	0.33	0.84	1.21	1.24	3.59	5.15

[a] PK parameters were calculated by non-compartmental analysis using WinNonlin, version 5.3.

In addition, several substituents were introduced to the *N*′-end of **8a**, and three new *N*′-substituted matrinic ethanamide (**9a–c**) analogs were designed and tested. As described in Table 1, all three compounds afforded good potency with EC_{50} values between 2.12 μmol/L and 5.09 μmol/L, but a high cytotoxicity with CC_{50} values between 16.3 and 42.7 μmol/L. Then, several groups were also added to the same position of **14d**, and a series of *N*′-substituted matrinic amides **18a–f** were also obtained. As anticipated, most of them (**18a–d**) exhibited promising anti-HCV activity with low micromolar EC_{50} values from 1.03 μmol/L to 4.89 μmol/L, and better therapeutic windows with SI from 81 to 132. The results indicated that the introduction of a proper substituent at the *N*′-end of matrinic amides could significantly enhanced the activity against HCV. In addition, two *N*′-acyl matrinic amine derivatives **23a–b** were also designed and tested. As depicted in Table 1, both of them had moderate activity with EC_{50} values of 14.4 and 5.0 μmol/L, and SI of 8.0 and 22, respectively. The results suggested that introducing a suitable group at the formyl group of matrinic amine derivatives might keep the antiviral activity against HCV.

Four representative compounds **14a**, **17** and **18a–b** with different structural features were chosen to examine their PK parameters in SD rats at a single dosage of 25 mg/kg *via* oral route. As indicated in Table 2 and Fig. 2, **18a** and **18b** had a poor PK profile with the area under the curve (AUC) of 0.21 and 1.21 μmol/L h, respectively Similarly, compound **14a** demonstrated a moderate PK parameter with AUC of 4.89 μmol/L h. As anticipated, **17** displayed excellent PK properties with the maximum concentration (C_{max}) and AUC of 3.97 μmol/L and 16.7 μmol/L h, respectively, indicating a good stability to metabolism *in vivo*. Compared with **17**, compounds **14a** and **18a–b** displayed an unsatisfying PK profile, which might be resulted from metabolically labile amido group at the *N*′-end.

Furthermore, single dose toxicity test for **17** was also carried out in mice. After compound **17** was given orally at a dose of 250, 500 or 1000 mg/kg, respectively, the mice were closely monitored for 7 days. No mouse died in the experiment, indicating that the LD_{50} value for **17** *via* oral route was over 1000 mg/kg. In addition, this treatment with **17** showed no effect on body weight of mice as well (data not shown). The results suggested that compound **17** was reasonably safe *in vivo*.

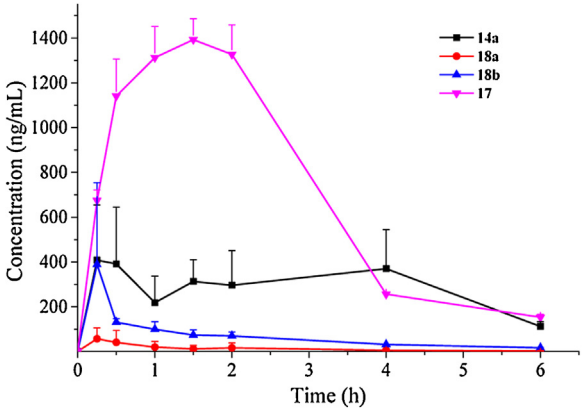

Fig. 2. Mean plasma concentration-*versus*-time curve of **14a**, **17** and **18a–b** after oral administration to mice ($n = 3$) at 25 mg/kg, respectively.

4. Conclusion

Taken together, 19 matrinic amide/ethanamine and matrinic acid/amine derivatives were synthesized and evaluated for their antiviral activity against HCV using compound **2** as the lead with novel mechanism against HCV. The SAR study indicated that the introduction of a suitable group at the *N*′-end of matrinic amide could greatly improve the anti-HCV potency. Among the newly synthesized compounds, matrinic acid analog **17** demonstrated good potency against HCV with SI of over 66, much better than that of the lead **2**. Moreover, it also displayed an excellent PK and safety profile *in vivo*, indicating good drug-like properties. Thus, compound **17** has been chosen as a novel anti-HCV agent for further investigation with the advantage of decreased chance of causing drug-resistant mutations.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 21472246 and 81321004) and the Beijing Natural Science Foundation (No. 7152097) and National Mega-Project for Innovation Drugs (No. 2012ZX09103101-037).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.03.006.

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