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Synthesis and *In Vitro* Anti-Influenza Evaluation of Rupestonic Acid Analogues: Effect of Configuration and Substitution at C (3)

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Abstract

Rupestonic acid is the main active compound in *Artemisia rupestris* L, which mainly grows in Xinjiang of China. To find its active group, a series of novel rupestonic acid 3-carbonyl analogues were prepared. The structures of the compounds were confirmed by spectral and high resolution mass spectrum. All compounds were evaluated for antiviral activity against influenza A (H3N2 and H1N1) and B viruses in MDCK cell cultures. The compounds displayed a confined structure-activity relationship. Compound **13** with allyl group was the most potent inhibitor against influenza A/H1N1 virus with an IC_{50} value of 4.27 μM and a SI value of 27.04. Dihydrogen amide **3** possesses the good potency against influenza B virus with an IC_{50} value of 5.5 μM and a SI value of 13.

Keywords: Rupestonic acid; Synthesis; Analogues; Anti-influenza activity

Anti-Influenza

Influenza is an infectious disease of respiratory tract caused by influenza viruses in humans throughout the world. Influenza viruses belongs to RNA viruses and composed of three general types: influenza A, B and C according to antigenicity of nucleoprotein [1,2]. Compared with influenza B and C, influenza A viruses are the most major pathogens. It exhibits 16 HA subtypes and 9 NA subtypes. Of them, H1N1, H3N2 and H1N2 subtypes cause acute respiratory disease in humans [3]. In the past for a long time, they had caused serious impact on global morbidity, mortality and economy. For example, Spanish flu (H1N1) in 1918, Asian influenza (H2N2) in 1957, Hong Kong influenza (H3N2) in 1968, avian influenza (H5N1) in 2007, swine influenza (H1N1) in 2009 and so on [4].

Currently, vaccination is the primary strategy for the prevention of influenza infections, but vaccines are ineffective against rapidly emerging mutant viral antigens [5]. In addition, the vaccine cannot effectively protect elderly people and children. Pharmacotherapy is another effective means of controlling the spread of influenza viruses. Until now, there are only four anti-influenza drugs approved for use by the United States FDA: M2 ion channel inhibitors (Amantadine and Rimantadine) and neuraminidase (NA) inhibitors (Oseltamivir and Zanamivir) [6]. The former are effective only against type A virus because of its self-structure and drug resistance has become widespread [7,8]. For the later, Oseltamivir phosphate (Tamiflu), an ethyl ester of GS4071, is an orally administered drug for the prophylaxis and treatment of human influenza A and B [9,10], whereas it has been reported that the H5N1 influenza virus has shown resistant to Oseltamivir [11,12]. Zanamivir is delivered by oral inhalation due to its poor oral bioavailability [13]. Thus, it is very urgent to search for new compounds with inhibitory activity against influenza.

2-(3,8-Dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl) acrylic acid (Rupestonic acid, **1**), first isolated from the dichloromethane extract of leaves of *Decachaeta scabrella* and named pechueloic acid, was isolated from dry *Artemisia rupestris* L (Chinese name Yi Zhihao) and purified using silica gel chromatograph. It is a multi-functional sesquiterpenoid compound [14]. During our previous studies, more than two hundred amide and ester derivatives of rupestonic acid have been synthesized by modifying the carboxyl group (C13) and the *in vitro* activities of these compounds against influenza viruses A and B were assayed [15-19]. Mechanism of action study and *in vivo* activity of selected candidate compounds are under way.

To study the structure-activity relationship (SAR) of rupestonic acid derivatives comprehensively, effect of modification at C (3) will be discussed in this research. The synthetic routes of C (3) analogues were depicted in Schemes 1-6.

As we know, carboxyl group possessed the high reactivity in organic chemical reaction and amide compounds were relatively more stable than carboxylic acid. In the beginning, amide was planned to prepare and protect carboxyl group. Amide **2** was formed from lead compound **1** and 4-chloroaniline using Bop (Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate)) and N-Hydroxybenzotriazole (HOBt) as the coupling reagents,4-(dimethylamino) pyridine (DMAP) as the catalyst and N,N-Diisopropylethylamine (DIPEA) as the base [20]. Meanwhile, reaction activity of carbonyl in α, β-unsaturated ketone was relatively low, so the next step was the obtainment of saturated amide **2**. It was carried out by hydrogenation over 10% Pd/C catalyst in EtOAC to afford dihydrogen amide **3** in 60% with high stereo selectivity, but it was found that C4=C5 in the five-membered ring did not hydrogenate. To finish the thorough hydrogenation of amide **2**, EtOH was selected as the solvent, whose polarity was stronger than that of EtOAC [21]. Interestingly, dechlorination production compound **4** has been generated. Its structure was confirmed by NMR and HRMS, similar results have been reported previously [22-24].

We, therefore, decided to find out another method to protect the carboxyl group. Methylation of rupestonic acid **1** and dimethyl sulfate using K_2CO_3 as the base afforded methyl rupestonate **5** in 98% [25]. Compound **5** was carried out by hydrogenation over 10% Pd/C catalyst

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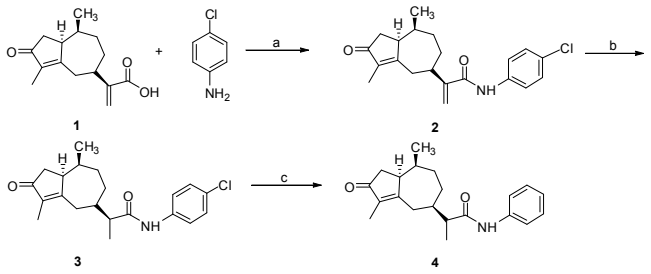
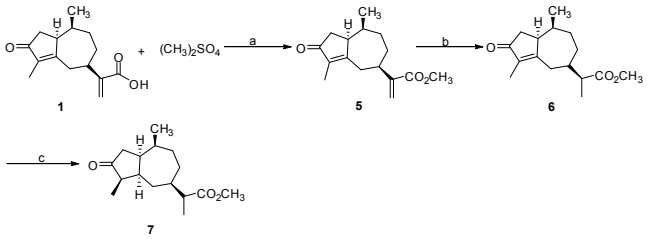
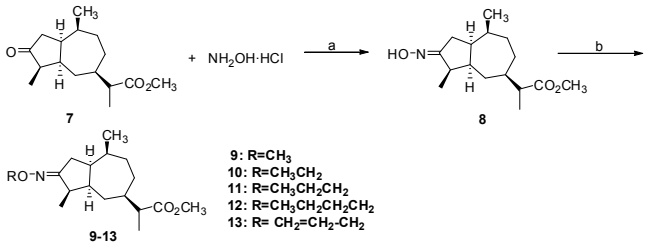


Scheme 1: Reagents and conditions: (a) Bop, HOBt, DIPEA, 60%; (b) H_2, 10% Pd/C, EtOAc; (c) H_2, 10% Pd/C, EtOH.



Scheme 2: Synthesis of tetrahydrogen methyl rupestonate. Reagents and conditions: (a) K_2CO_3, CH_2Cl_2, 98%; (b) H_2, 10% Pd/C, EtOAc, 83%; (c) H_2, 10% Pd/C, EtOH, 70%.



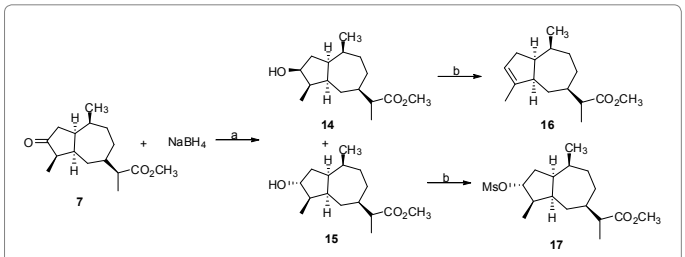
Scheme 3: Synthesis of ketoximes ethers. Reagents and conditions: (a) NaOAc, MeOH, 98%; (b) appropriate alkyl iodide, NaH, THF, 48-89%.

in EtOAC or EtOH to afford dihydrogen methyl rupestonate **6** or tetrahydrogen methyl rupestonate **7** in 83% or 70%, respectively [24]. As can be seen, the polarity of the solvent played an important role in the hydrogenation process.

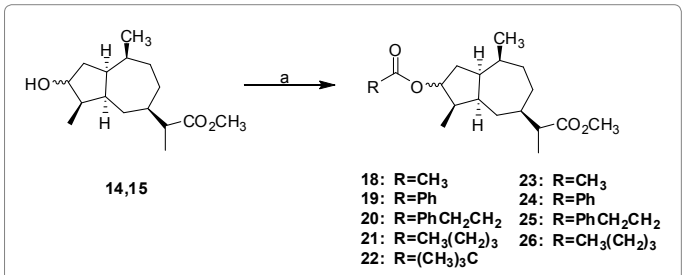
Compound **7** served as the starting materials for the preparation of the C(3)-modified analogues **9**-**31**. Various ketoximes ethers (**9**-**13**), esters (**18**-**25**) and ethers (**27**-**31**) analogues were prepared at this site and assayed *in vitro* anti-influenza activity.

O-ketone oxime **8** were obtained by starting with compound **7** and $NH_2OH{\cdot}HCl$ using NaOAc as the base in near quantitative yield (98%). And then, it was treated with appreciate alkyl iodide to obtain ketoximes ethers **9**-**13** [26].

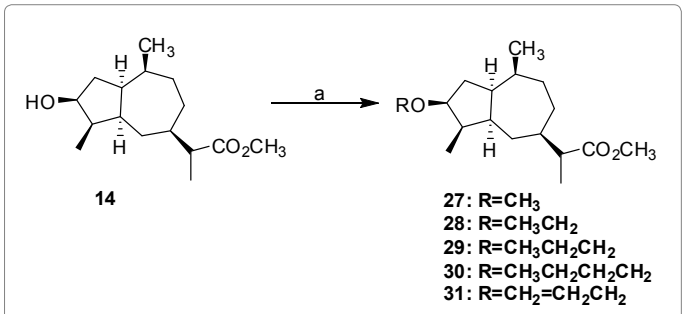
In Scheme 4, treatment of compound **7** with $NaBH_4$ afforded two epimeric alcohols **14** (43%) and **15** (45%), which were easily separated by silica gel chromatography. Alcohol **14** with excess methane sulfonyl chloride/pyridine in CH_2Cl_2 at 0°C afforded alkene **16** in 70% yield; on the other hand, treatment of its epimer **15** by quick mesylation under the same condition afford the expected methane sulfonate **17.** This was consistent with trans-elimination rule of alcohol. Unfortunately, the substitution reaction between compound **17** and sodium benzene thiolate with different substitution failed.



Scheme 4: Reagents and conditions: (a) MeOH, 98%; (b) MsCl, Et_3N, CH_2Cl_2.



Scheme 5: Synthesis of esters. Reagents and conditions: (a) appropriate acyl chlorides, pyridine, 32%-86%.



Scheme 6: Synthesis of ethers. Reagents and conditions: (a) appropriate alkyl iodine, Ag_2O, CH_3CN, 47%-71%.

Standard acylation condition (appropriate acyl chlorides, pyridine) was then carried out and yielded the desired esters **18**-22 from compound **14** and **23**-**26** from **15** with yields ranging from 32-73% (Scheme 5) [26]. As can be seen, the same condition was ineffective using compound **15** and *tert*-butyl formyl chloride as the starting materials. This may be attributed to the space steric hindrance of *tert*-butyl. Incorporation of ethers at C(3) was accomplished according to Scheme 6. Treatment of **14** with the appropriate alkyl iodide in the present of Ag_2O created the corresponding ethers **27**-**31.** Our attempts to prepare ethers failed using compound **15** as the starting material under the same conditions.

Spectra data (^1H NMR, ^{13}C NMR and HRMS) consistent with the proposed structures were obtained for all the compounds prepared in this study. To determine the potential activity of compounds **2**-**31**, they were preliminarily assayed *in vitro* against influenza A (H3N2, H1N1) and B viruses [27]. The inhibition and selectivity of these compounds were listed in Table 1.

As can been seen from Table 1, most of the target compounds showed some potency against influenza H1N1 virus, but most did not show obvious activity against influenza H3N2 and B viruses. Among of them, parent compound **1** presented the best activity against influenza H3N2, with an IC_{50} value of 25.77 μM and a SI value of 180.6. Compound **13** with allyl group was the most potent analogy among

Compd.	R	TC_{50} (μM)[a]	Against influenza H3N2 virus		Against influenza H1N1 virus		Against influenza B virus	
			IC_{50} (μM)[b]	SI[c]	IC_{50} (μM)[b]	SI[c]	IC_{50} (μM)[b]	SI[c]
1[d]	—	4653	25.77	180.6	>1344	—[e]	>4032	—[e]
Amides								
2	—	34.5	>11.5	—[e]	>11.5	—[e]	>11.5	—[e]
3	—	71.4	>34.4	—[e]	26.6	2.68	5.5	13.00
4	—	1776.5	1026.9	1.73	493.1	3.60	>32.5	—[e]
Esters								
5	—	294.0	27.2	10.81	81.6	3.60	>141.4	—[e]
6	—	542.3	108.9	4.98	81.0	6.69	60.3	9.00
7	—	417.7	>139.2	—[e]	108.0	3.87	139.2	3.00
Ketoxime ethers								
8	H	395.4	>131.8	—[e]	34.6	11.43	131.8	3.00
9	CH_3	161.8	>41.86	—[e]	>41.86	—[e]	>41.9	—[e]
10	CH_3CH_2	69.2	>13.33	—[e]	13.33	5.19	>13.3	—[e]
11	$CH_3(CH_2)_2$	66.2	>38.24	—[e]	16.42	4.03	>38.2	—[e]
12	$CH_3(CH_2)_3$	329.7	>109.9	—[e]	85.2	3.87	109.9	3.00
13	CH_2=CH-CH_2	115.4	>38.5	—[e]	4.27	27.04	12.5	9.23
Alcohols								
14	—	287.5	>138.2	—[e]	>138.2	—[e]	>139.2	—[e]
15	—	718.1	>414.6	—[e]	414.6	—[e]	>414.6	—[e]
Alkene								
16	—	256.6	>148.2	—[e]	63.64	4.03	148.3	1.73
Methanesulfonate								
17	—	963.4	>321.2	—[e]	198.6	4.85	321.1	3.00
Esters								
18	CH_3	238.6	>72.3	—[e]	46.8	5.10	>46.5	—[e]
19	Ph	207.1	>99.6	—[e]	69.03	3.00	>99.6	—[e]
20	$PhCH_2CH_2$	1940.2	110.2	17.61	215.6	9.00	>277.8	—[e]
21	$CH_3(CH_2)_3$	1969.8	>946.7	—[e]	83.15	23.69	947.0	2.08
22	$(CH_3)_3C$	182.2	>105.2	—[e]	15.39	11.84	65.07	2.80
15	H	718.1	>414.6	—[e]	414.6	—[e]	>414.6	—[e]
23	CH_3	90.77	>13.3	—[e]	13.00	6.98	>13.3	—[e]
24	Ph	298.68	>99.6	—[e]	33.19	9.00	99.56	3.00
25	$PhCH_2CH_2$	481.1	>92.6	—[e]	>92.6	—[e]	>92.6	—[e]
26	$CH_3(CH_2)_3$	406.7	105.1	3.87	105.1	3.87	>105.2	—[e]
Ethers								
27	CH_3	131.3	>43.8	—[e]	33.94	3.87	>43.8	—[e]
28	CH_3CH_2	72.23	>41.7	—[e]	32.39	2.23	>41.7	—[e]
29	$CH_3(CH_2)_2$	206.9	>119.5	—[e]	92.80	2.23	>119.5	—[e]
30	$CH_3(CH_2)_3$	198.0	>114.3	—[e]	88.79	2.23	88.8	—[e]
31	CH_2=CH-CH_2	7.73	>4.45	—[e]	>4.45	—[e]	>4.45	—[e]
Ribavirin	—	1278	3.9	329.4	1.9	665.6	14.7	86.9
Oseltamivir	—	1260	1.1	1135.1	15.5	81.3	>500	—[e]

[a]50% cytotoxic concentration; [b]50% inhibitory concentration, determined by CPE inhibition assay; [c]Selectivity Index (TC_{50}/IC_{50}); [d]Parent compound; [e]The SI cannot be calculated, because the highest concentration tested was less than the IC_{50}.

Table 1: Chemical structures and antiviral activity of Rupestonic acid analogues against influenza A (H3N2 and H1N1) and B viruses.

the series against influenza H1N1 with an IC_{50} value of 4.27 μM and a SI value of 27.04, which was much better than that of Oseltamivir. Dihydrogen amide **3** showed the best activity against influenza B with an IC_{50} value of 5.5 μM and a SI value of 13, which was about 3 times higher than Ribavirin.

When rupestonic acid was converted into amide **2**, **3** and **4**, it was found that the activity against influenza H3N2 decreased obviously compared with parent compound **1**. For compound **4**, it can be seen that removal of the chlorine group by hydrogenation reduced the toxicity. For methyl ester compound **5**, we can see the activity was very close to that of compound **1**, but its toxicity increased dramatically (TC_{50}=294 μM). But when C_4=C_5 or C_{11}=C_{13} hydrogenated, dihydrogen methyl rupestonate **6** (TC_{50}=542.3 μM) or tetrahydrogen methyl rupestonate **7** (TC_{50}=417.7 μM) possessed lower toxicity than methyl ester compound **5** (TC_{50}=294.0 μM).

It can be seen that the size of the alkyl substituents in the ketoximes ethers (**9**-**13**) was critical for the activity. It was noted that the activity against influenza H1N1 virus was in the order: CH_2=CH-CH_2(**13**)> CH_3CH_2(**10**)> $CH_3(CH_2)_2$(**11**)> H(**8**)> CH_3(**9**)> $CH_3(CH_2)_3$(**12**). Of these, compound **13** linked to allyl group showed the best activity

against influenza H1N1 and B viruses with an IC_{50} value of 4.27 μM and 12.5 μM respectively. As we know, oxime ether structure was often selected as the active group in drug research and discovery. So, the C=C of CH_2=CH-CH_2 and C=N of oxime ether may strong the interaction of compound **13** with the neuraminidase of the influenza virus. All of these derivatives did not show the activity against influenza H3N2. For epimeric alcohol **14** and **15**, it was observed that **14** (TC_{50}=287.5 μM) was more toxic than **15** (TC_{50}=718.1 μM).

Similar SAR patterns were observed in the esters (**18**-**25**). There were obvious activity difference between enantiomers, for example, compound **18** and **23**, **19** and **24**, **20** and **25, 21** and **26.** Compound **23** with methyl remained the best activity against influenza H1N1 with an IC_{50} value of 13.00 μM. Compound **22** with tertiary butyl possessed the best activity against influenza B with an IC_{50} value of 65.07 μM. It can be exemplified by the relative contribution of related R groups to anti-influenza H1N1 activity between **18**-**22** as follows: $(CH_3)_3C$(**22**)> CH_3(**18**)> Ph(**19**)> $CH_3(CH_2)_3$ (**21**)>$PhCH_2CH_2$(**20**). For ethers **27**-**31**, unfortunately, they did not show obvious activity against influenza A and B viruses, although their structures were very similar to that of ketoxime ethers **8**-**13**. And we can see, the structures of compound **27**-**31** were very close to the saturated molecules. So due to the lack of active functional group in ether, they showed very weak anti-influenza virus activity. Meanwhile, it can conclude that the functional group-ketoxime played a very important role against influenza virus.

In summary, a series of novel rupestonic acid analogues were designed, synthesized and evaluated for their *in vitro* anti-influenza activity. Several compounds were found to possess moderate influenza inhibitory activity, although in all cases, measured activities were lower than that of Oseltamivir and Ribavirin. The most active compound **13** (IC_{50} = 4.27 μM) has good anti-influenza H1N1 activity which is fourfold more potent than positive drug Oseltamivir (IC_{50} = 15.5 μM) and it also showed better anti-influenza B activity than positive drug Ribavirin (IC_{50} = 14.7 μM). Our study indicated that rupestonic acid analogues could show potent inhibitory activity and the research finding will be used to design novel influenza inhibitors.

The Procedure for the Anti-Influenza Virus Assay

Each compound was dissolved in DMSO at an initial concentration of 1000 μg/mL and then diluted 3-fold successively to obtain 8 different concentrations (333.33, 111.11, 37.04, 12.35, 4.12, 1.37, 0.46 and 0.15, 0.05 μg/mL, respectively) as stock solutions for the following experiments. (2) Madin-Darby canine kidney cells (MDCK) were seeded in 96-well trays and cultured at 37°C in a humidified CO_2 incubator (95% air, 5% CO_2) for 24 h. Then, the cells were infected with influenza A virus with 10^{-4} [316 times the 50% tissue culture infective dose ($TCID_{50}$)] and with influenza B virus with $1/210^{-2}$ [158 times of the 50% tissue culture infective dose ($TCID_{50}$)], respectively. All of infected tissue culture plates (96 wells) were incubated at 37°C for 2 h, and then the medium was removed. Subsequently, 100 μL aliquots of the solutions with different concentrations of each compound were added to the wells (one per well), and the plates were incubated again for 36 h at 37°C. Then, the inhibition of the virus-induced cytopathic effect (CPE) for each sample was recorded relative to the cell control and the virus control. The 50% cell-inhibitory concentration (IC_{50}) values of active compounds were calculated accordingly. The inhibitory potentials of rupestonic acid derivatives were comparable to those of the parent compound and the commercial drugs Ribavirin (RBV) and Oseltamivir.

Acknowledgements

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