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1-Aryl-tetrahydroisoquinoline analogs as active anti-HIV agents in vitro

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Abstract—A series of 1-aryl-6,7-dihydroxyl(methoxy)-1,2,3,4-tetrahydroisoquinolines (compounds **1**–**36**) were synthesized via Pictet–Spengler cyclization. All the synthesized compounds were assayed for activities against HIV-1_{IIIB} in C8166 cell cultures by MTT method for the first time. The results of the anti-HIV screening revealed that 6,7-dihydroxytetrahydroisoquinolines possessed higher selective index than 6,7-dimethoxyl analogs due to the significantly decreased cytotoxicities. Compounds **6**, **24**, and **36** showed potent anti-HIV activities with EC_{50} values of 8.2, 4.6, and 5.3 μM respectively, and the cytotoxicities (CC_{50}) of these three compounds were 784.3, 727.3, and 687.3 μM, which resulted in SI values larger than 95, 159, and 130 respectively.

1,2,3,4-Tetrahydroisoquinoline (THIQ) was a common core structure of many alkaloids isolated from natural sources and showed antitumor,[1] antimicrobial,[2] and other biological activities.[3–7] The recent success in total synthesis of ecteinascidin 743[8,9] and its human clinical trials[10,11] have shed light on this class of natural products.

Prompted by a report of the anti-human immunodeficiency virus (HIV) activity of michellamine B (Fig. 1), a naphthylisoquinoline alkaloid dimmer from *Ancistrocladus korupenis*,[12] evaluations of natural THIQs as inhibitors of HIV-1 were continuously reported in the literatures. The rigid THIQ derivatives chelidoneme,[13] *O*-methyl psychotrine sulfate,[4] and magnoflorine[13] inhibited HIV-1 target at reverse transcriptase (RT). More recently, a series of active anti-HIV benzyl THIQ derivatives were isolated from the leaves of *Nelumbo nucifera*, among which *R*-coclaurine inhibited HIV replication in H9 cell with an EC_{50} value of 0.8 μg/mL (selective index > 125).[14] Besides, Iwasa and colleagues reported that 1-methyl-6,7-dihydroxytetrahydroisoquinoline (compound **A**, Fig. 1) still possessed an EC_{50} value of 0.117 μg/mL (SI = 181) in H9 cell.[2] During the course of our continuous search for anti-HIV compounds from natural sources, it was suggested that compound **B**, an isomer of **A**, showed 48% inhibitory ratio against HIV-1 RT at 210 μg/mL.[15]

Based on the anti-HIV activities of THIQs derivatives reported previously, our interest in this study was to synthesize simple 1-aryl-tetrahydroisoquinoline analogs (**C**) and assess these compounds as anti-HIV agents to identify active compounds and reveal structure–activity relationship (SAR) trends. The syntheses of compounds **C** focused on the replacement of methyl (C-1) and hydroxyl (C-6 and C-7) in compound **A** by various aromatic moieties and methoxyl group, respectively.

THIQs were generally prepared as racemates by acid catalyzed Pictet–Spengler cyclization.[16,17] On the basis of this method, compounds **C** (**1**–**36**) (Table 1) were synthesized as outlined in Scheme 1. When R was hydroxyl group, dopamine hydrochloride and aromatic aldehyde were selected as starting materials. A solution of dopa-

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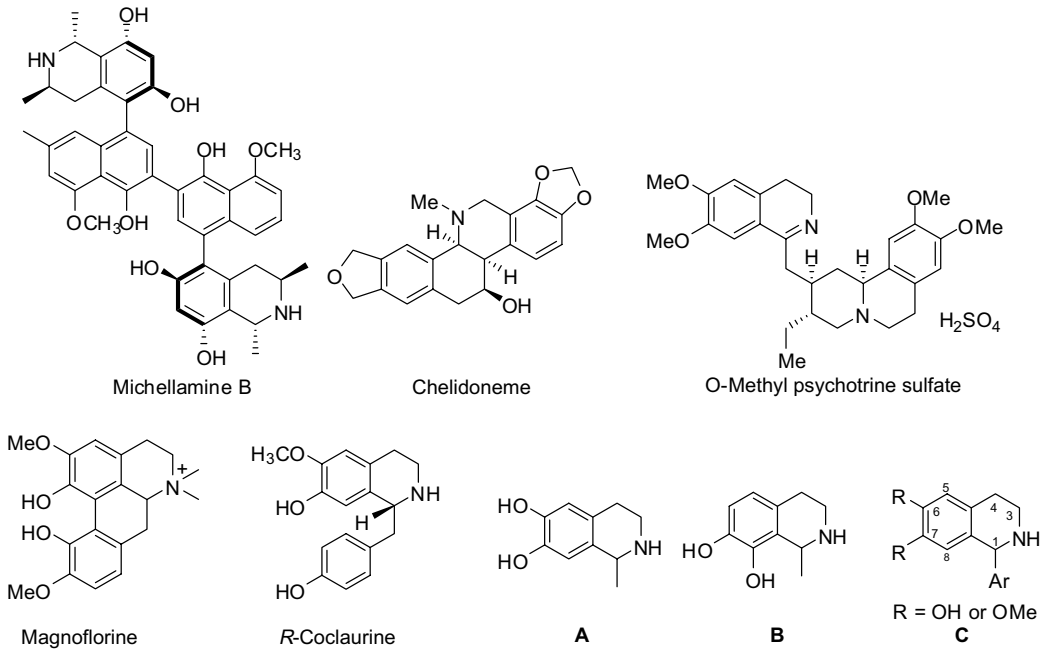


Figure 1. Structures of some THIQ derivatives.

mine hydrochloride and aromatic aldehyde in dichloromethane (DCM) was stirred under nitrogen atmosphere for 72 h to afford the target compounds in moderate to good yields after column chromatography separation (Table 1).

When the starting material changed to 3,4-dimethoxyphenylethylamine, the one-pot procedure only afforded the target compounds in poor yields after a screening of various Bronsted acid catalysts including 4-methylphenylsulfonic acid,[18] trifluoroacetic acid (TFA),[19] and trifluoromethylsulfonic acid (TFSA).[20] A further literature survey demonstrated that Pictet–Spengler cyclization would be favored if the imine was used as substrate directly.[21–23] As a result, the methoxyl THIQs were synthesized in two steps: imine intermediates were obtained without further purification. Then, the already usable imines were dissolved in TFA and heated to reflux[23] or 120 °C in Schelenk sealed tube for 4 h to afford target compounds in good yields after column chromatography. It should be noted that refluxing the corresponding imines in TFA for 4 h at normal boiling temperature only afforded the compounds **7**, **9**, **11**, and **29** in very poor yields. The reactions performed at higher temperature (120 °C in Schelenk sealed tube for 4 h) gave good yields for the electron-rich imines.

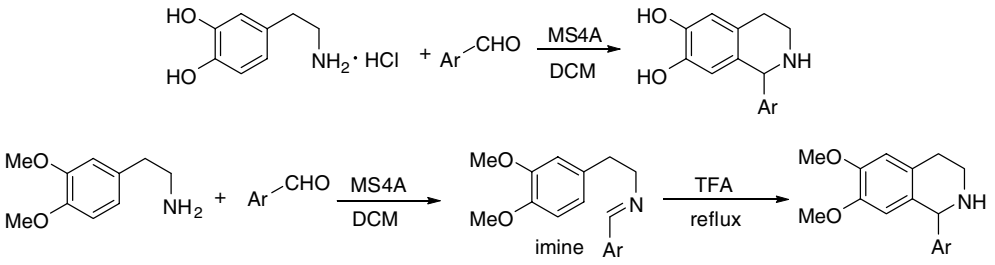
According to the previous literatures reported by other research groups, 1-aryl-tetrahydroisoquinolines displayed various biological activities including antibacterial,[23] bronchodilator,[24] and anticonvulsant[25] properties. Herein, Compounds **1**–**36** were evaluated for activity against HIV-1_{IIIB} in C8166 cell cultures for the first time. AZT (zidovudine) was included as a reference compound. The anti-HIV activities (EC_{50}), cytotoxicities (CC_{50}), and selective index (SI) for the tested compounds were summarized in Table 1. The results suggested that the 6,7-dimethoxy derivatives only exhibited weak anti-HIV activities (SI < 10) except compound **7**. O-Demethylation led to significantly decreased cytotoxicities with higher SI values. For example, 1-*para*-methylphenyl-6,7-dihydroxytetrahydroisoquinoline (**6**) showed a CC_{50} value of >784.3 μM (SI > 95), while its methoxyl derivative **5** possessed a CC_{50} of 280.7 μM. In addition, hydroxyl groups bond to C-6 and C-7 might play an important role in potent anti-HIV activity as to the title compounds. For example, compound **24** exhibited an EC_{50} of 4.6 μM (SI > 159), but its methoxyl derivative **23** only showed an EC_{50} of 31.8 μM. When Ar moiety located at C-1 changed to 2-furyl, 2-pyridinyl or naphthyl, compounds **30**, **32**, and **36** still had antiviral activities. Especially, compound **36** showed anti-HIV activity with EC_{50} and CC_{50} values of 5.3 and >687.3 μM, respectively, resulting in a SI value of >130.

The above-mentioned anti-HIV activity information suggested the importance of hydroxyl groups at C-7 and C-8 for minimal cytotoxicities and potent antiviral activities. But there were exceptions, which were the cases for the inactive hydroxyl compounds **14** and**34**. Compound **14** (Ar = *para*-trifluoromethylphenyl) showed EC_{50} and CC_{50} values of 8.52 and 13.07 μg/mL respectively (SI = 1.5), indicating that the trifluoromethyl group was a cytotoxic moiety compared with compound **6** (Ar = *para*-methylphenyl). Compound **34**, the 1-naphthyl analogue, only exhibited SI value of 1.9 (CC_{50} = 47.4 μM). Interestingly, the 2-naphthyl derivative **36** showed an obviously increased SI value of >130 due to the decreased cytotoxicity (CC_{50} > 687.3 μM) and increased anti-HIV activity (EC_{50} = 5.3 μM).

Table 1. Structures, physical data, and anti-HIV activities of compounds **C**[a]

Compound **C**	R	Ar	Yields (%)[b]	State	Mp (°C)	EC_{50}[c] (μM)	CC_{50} (μM)[d]	SI[e] (CC_{50}/EC_{50})
1[23]	–OMe	Phenyl	72	White solid	77–80	119.6	293.5	2.4
2[24]	–OH	Phenyl	65	Yellow solid	115–117	67.3	>829.9	>12
3	–OMe	2-Methylphenyl	75	White solid	68–70	42.5	197.0	4.6
4	–OH	2-Methylphenyl	59	Yellow solid	109–113	61.9	>784.3	>13
5[26]	–OMe	4-Methylphenyl	60	White solid	84–86	67.3	280.7	4.2
6[27]	–OH	4Methylphenyl	77	White solid	112–115	8.2	>784.3	>95
7[28]	–OMe	2-Methoxyphenyl	78	Viscous oil	—	45.9	555.1	12
8	–OH	2-Methoxyphenyl	85	Yellow solid	220–222	42.2	>738.0	>18
9[29]	–OMe	4-Methoxyphenyl	77	Viscous oil	—	127.2	312.1	2.5
10[30]	–OH	4-Methoxyphenyl	68	Pale yellow solid	94–96	34.1	>738.0	>22
11	–OMe	2,4-Dimethoxyphenyl	73	Viscous oil	—	43.8	227.3	5.2
12	–OH	2,4-Dimethoxyphenyl	55	Pale yellow solid	109–112	46.5	>664.4	>14
13[26]	–OMe	4-Trifluoromethylphenyl	71	White solid	137–139	27.8	30.9	<1
14	–OH	4-Trifluoromethylphenyl	80	White solid	78–80	27.6	42.3	1.5
15[31]	–OMe	4-Bromphenyl	72	White solid	109–113	16.9	37.9	2.2
16	–OH	4-Bromphenyl	75	Pale yellow solid	116–118	36.2	>625.0	>18
17[25]	–OMe	3-Bromophenyl	74	White solid	80–82	43.5	106.7	2.4
18	–OH	3-Bromophenyl	62	Yellow solid	93–96	53.5	>625	>12
19[32]	–OMe	2-Bromophenyl	73	Viscous oil	—	31.3	89.0	2.8
20	–OH	2-Bromophenyl	67	Yellow solid	112–114	23.7	>625	>26
21	–OMe	2-Fluorophenyl	75	Viscous oil	—	69.0	175.4	2.8
22	–OH	2-Fluorophenyl	61	Yellow solid	183–185	58.4	>772.2	>13
23[25]	–OMe	3-Chlorophenyl	64	White solid	83–85	31.8	183.6	5.9
24	–OH	3-Chlorophenyl	62	Yellow solid	114–116	4.6	>727.3	>159
25[28]	–OMe	2-Chlorophenyl	77	Viscous oil	—	58.4	248.7	4.3
26[29]	–OH	2-Chlorophenyl	56	Yellow solid	109–111	51.8	>727.3	>14
27[26,33]	–OMe	4-Nitrilephentyl	76	White solid	110–112	60.1	46.2	7.7
28[34]	–OH	4-Nitrilephentyl	78	White solid	208–210	53.7	>751.9	>14
29	–OMe	2-Furyl	68	Viscous oil	—	152.4	572.5	3.8
30	–OH	2-Furyl	63	Yellow solid	83–85	61.7	>865.8	>14
31[35]	–OMe	Pyridin-2-yl	76	Viscous oil	—	171.2	444.5	2.8
32	–OH	Pyridin-2-yl	80	Yellow solid	215–217	48.4	>826.4	>11
33	–OMe	1-Naphthyl	76	Viscous oil	—	22.6	64.8	2.9
34	–OH	1-Naphthyl	68	Yellow solid	236–238	33.2	47.4	1.9
35	–OMe	2-Naphthyl	76	White solid	93–96	6.9	54.6	7.9
36	–OH	2-Naphthyl	63	Pale yellow solid	110–113	5.3	>687.3	>130
AZT[f]	—	—	—	—	—	0.011	>749	>68,091

[a] Anti-HIV data represent the mean values of two separate experiments.
[b] Isolated yields.
[c] Effective concentration required to protect C8166 cells against the cytopathogenicity of HIV by 50%.[36]
[d] Cytostatic concentration required to reduce C8166 cell proliferation by 50% tested by MTT method.[36]
[e] Selectivity index; ratio CC_{50}/EC_{50}.
[f] AZT (zidovudine) was used as positive control.



Scheme 1. Synthesis of target compounds **C**.

Structure modification of compounds **C** had led to three active anti-HIV compounds **6**, **24**, and **36**. Based on the previous literature,[37] THIQs generally inhibited HIV-1 replication as non-nucleoside reverse transcriptase inhibitors (NNRTIs). These three compounds that showed potent anti-HIV-1 activity were also evaluated on their inhibitory activity of recombinant HIV-1 RT, but they only showed 28%, 20%, and 30% inhibitory rate

to HIV-1 RT at a concentration of 200 μg/mL, respectively. The suboptimal enzymatic activities of these assayed compounds suggested that further study on the possible mechanisms of action is needed to provide the detailed properties of 1-aryl THIQ as anti-HIV agents.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.02.040.

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36. C8166 cells were maintained in RPMI-1640 supplemented with 10% heat-inactivated newborn calf serum (Gibco), The cells used in all experiments were in log-phase growth. 3′-Azido-3′-deoxythymidine (AZT), the positive control, was purchased from Sigma (USA).
Syncytium reduction assay: In the presence of 100 μL of various concentrations of compounds, C8166 cells (4×10^5 mL^{-1}) were infected with HIV-1_{IIIB} at a multiplicity of infection (MOI) of 0.06. The final volume per well was 200 μL. AZT was used as a positive control. After 3 days of culture, the cytopathic effect (CPE) was measured by counting the number of syncytia (multinucleated giant cell) in each well under an inverted microscope. Percentage inhibition of syncytial cell number in treated culture to that in infected control culture and 50% effective concentration (EC_{50}) was calculated.
Cytotoxicity assay: The cellular toxicity of compounds on C8166 cells was assessed by MTT methods. Briefly, cells were seeded on a microplate in the absence or presence of various concentrations of compounds in triplicate and incubated at 37 °C in a humid atmosphere of 5% CO_2 for 72 h. The supernatants were discarded and MTT reagent (5 mg/mL in PBS) was added to each well, then incubated for 4 h, 100 μL of 50% DMF-20% SDS was added. After the formazan was dissolved completely, the plates were read on a Bio-Tek ELx 800 ELISA reader at 595/630 nm. The cytotoxic concentration that caused the reduction of viable cells by 50% (CC_{50}) was calculated from dose–response curve.
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