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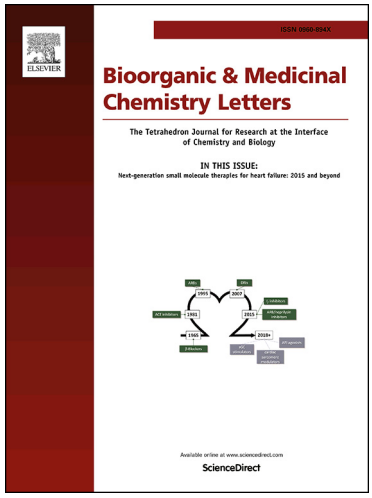

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PII: S0960-894X(18)30361-5
DOI: https://doi.org/10.1016/j.bmcl.2018.04.049
Reference: BMCL 25796

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 28 February 2018
Revised Date: 13 April 2018
Accepted Date: 18 April 2018

Please cite this article as: Liu, X., Chen, P., Li, X., Ba, M., Jiao, X., Guo, Y., Xie, P., Design, synthesis and biological evaluation of substituted (+)-SG-1 derivatives as novel anti-HIV agents, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.04.049

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Design, synthesis and biological evaluation of substituted (+)-SG-1 derivatives as novel anti-HIV agents

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
HIV
NNRTIs
SG-1
Structure-activity relationship
NNRTI-resistant

ABSTRACT

SG-1 was previously identified as a potent Non-nucleoside reverse transcriptase inhibitors (NNRTI) which works through inhibition of reverse transcriptase (RT) RNA-dependent DNA polymerase activity via a direct binding event. To further investigate the relationship between its structure and activity, four series of novel analogues were designed and synthesized with 12 of them inhibiting HIV-1 replication with IC_{50}s in the range 0.09 to 6.71 μM. Compound **4b**, **4c**, **4f**, **2** and **6b** were further tested on two NNRTI-resistant HIV-1 strains and one NNRTI-resistant superbug. The result showed that RT- E138K/M184V mutant virus conferred 4.7 to 9.1-fold resistance to **4c**, **4f**, **2** and **6b**, but only showed slight resistance to **4b** (2-fold) which was better than SG-1.

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Human immunodeficiency virus type 1 (HIV-1) is the etiologic agent of acquired immunodeficiency syndrome (AIDS) and there are currently more than 35 million individuals worldwide living with HIV-1.[1] Reverse transcriptase (RT) of HIV-1 is an important target for anti-HIV drug discovery. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are non-competitive inhibitors of RT's and serve as pivotal components of highly active antiviral therapies (HAART).[2] The first-generation of NNRTIs, nevirapine (NVP) and efavirenz (EFV) were approved in the late 20th century. After more than 20 years of continuous clinical use, the incidence of NNRTI-resistant mutations observed from clinical isolates obtained from patients suffering with HIV-1.[3] Moreover, some major NNRTI-resistant viruses, such as RT-K103N and RT-Y188L, showed strong cross-resistance between NVP and EFV.[4] To combat these NVP/EFV-resistant viruses, second generation NNRTIs such as Etravirine (ETR) and Rilpivirine (RPV) were developed. These diarylpyrimidine containing (DAPY) NNRTIs are not only potent to wild type RT, but also show higher genetic barrier to the first-generation-NNRTI-resistance mutations since both are able to bind RT in multiple conformations.[5] However, it was later found that RT-E138K and M184V mutations emerged in patients when treated with Tenofovir (TDF)/Emtricitabine (FTC)/ Rilpivirine. HIV-1 carrying RT-E138K/M184V mutations are known to be resistant to both NNRTIs (RPV and ETR) and NRTIs (FTC and 3TC). Furthermore, it was reported that when HIV RT contained E138K/M184V/I, the virus exhibited a higher replication capacity compared to the wild type virus.[6] Since this 'super' mutant HIV-1 occurred in patients treated with the second generation of NNRTIs, the discovery and evaluation of novel NNRTIs discovery is still of critical importance.

Traditionally natural products (NP) have played an important role in drug discovery and have proven to be vital source of numerous drug leads. Many classes of natural products have been shown to exhibit anti-HIV activity such as alkaloids, chromans, flavonoids, lignins, triterpenes and coumarins.[7,8] Recently, we reported on the discovery of SG-1, a cyclolignan semi-synthesized from a lignin isolated from *Machilus robusta*, as a potent NNRTI with submicromolar concentration inhibitory activity against RT polymerase.[9]

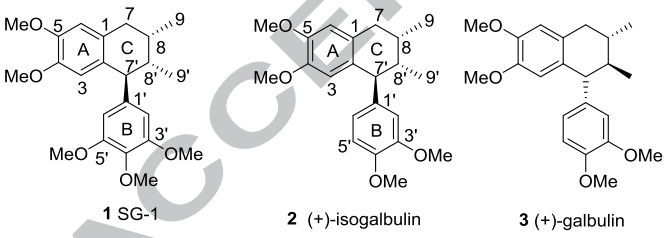


Fig.1. The structures of SG-1, (+)-isogalbulin (**2**) and (+)-galbulin (**3**)

In our previous report, we synthesized the natural products (+)-isogalbulin (**2**) and (+)-galbulin (**3**) (Fig. 1).[10] Considering the structure similarity of the (+)-isogalbulin (**2**), (+)-galbulin (**3**) and SG-1, we initially tested their activity against HIV-1. The results showed that (+)-isogalbulin (**2**) had good inhibitory activities against HIV-1 with an IC_{50} value (using VSV-G/HIV-1 infection assay) of 1.07 μM, while (+)-galbulin (**3**) showed no anti-HIV activity at 10 μM, and this data illuminated some clear SAR trends. The 5'-OMe group in aromatic ring B and the absolute configuration at C7' and C8' may be important for the activity. Based on this hypothesis result, we designed and synthesized four series of novel analogues (**4**, **5**, **6**, **7**) to further explore this interested and potentially useful structure-activity relationship (SAR) (Fig. 2).

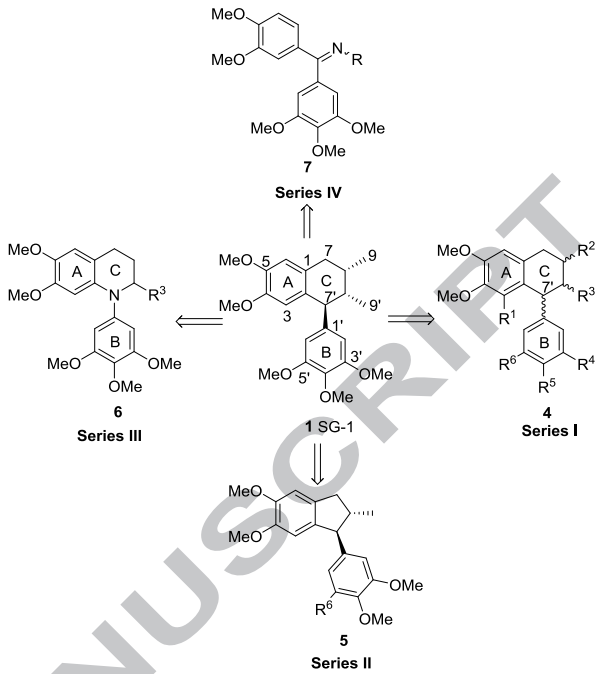
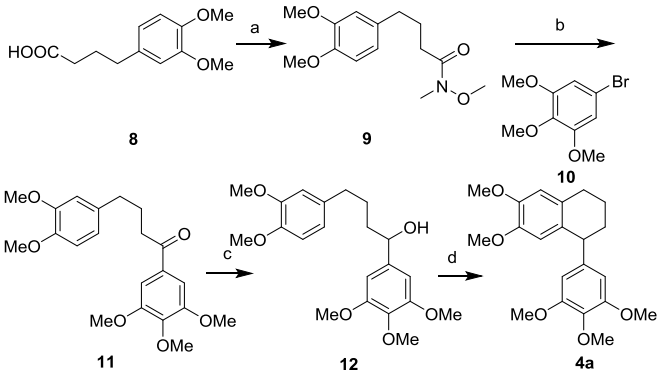


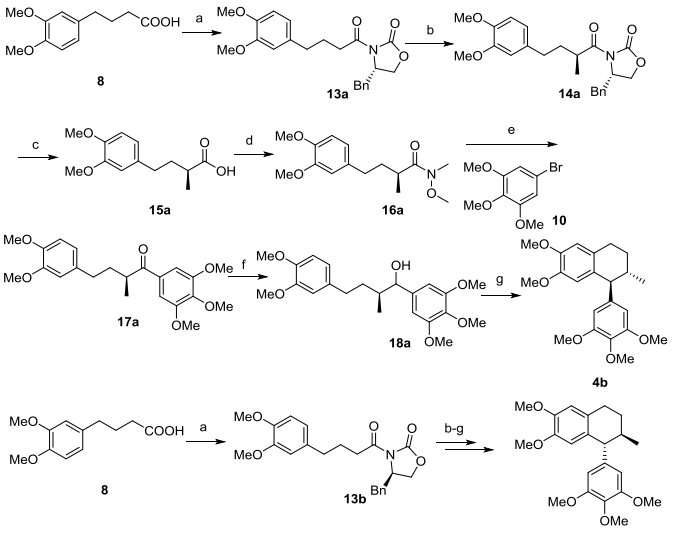
Fig.2. The structures of compound **1**, **4**, **5**, **6** and **7**

The synthetic strategies to access analogues **4** are described in Scheme 1-4. The target compound **4a** was synthesized using 4-(3, 4-dimethoxyphenyl) butanoic acid **8** as the starting material (Scheme 2). **8** was converted to the Weinreb amide **9** using EDCI as coupling agent in excellent yield.[11] Nucleophilic addition of the Weinreb amide **9** followed by reduction gave the alcohol **12**. Cyclization of **12** with HF-pyridine produced **4a**.



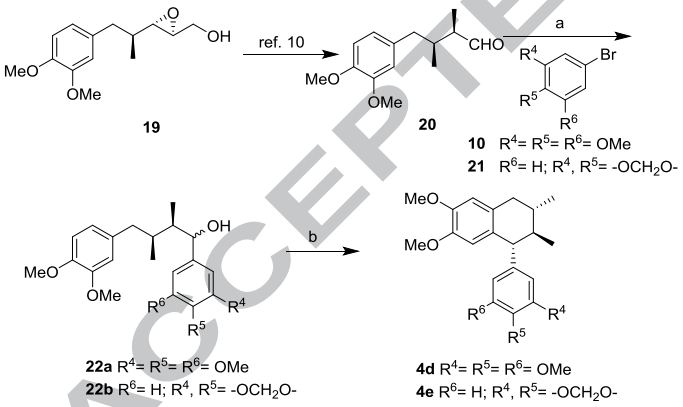
Scheme 1. Synthesis of compound **4a.** Reagents and conditions: (a) EDCI, HOBT, N, O-Dimethylhydroxylamine hydrochloride, 4-Methylmorpholine, CH_2Cl_2, 74%; (b) *n*-BuLi, THF, −78°C, 55%; (c) $NaBH_4$, MeOH, rt, 87%; (d) HF-pyridine, CH_3CN, rt, 60%.

The target compounds **4b** and **4c** were prepared through a different synthetic strategy (Scheme 2). Compound **4b** was prepared from 4-(3,4-dimethoxyphenyl) butanoic acid **8** which could be easily transformed to **13a** (Scheme 2). An asymmetric alkylation reaction of compound **13a** produced compound **14a**. Removal of the chiral auxiliary under hydrolysis condition followed by coupling and nucleophilic addition afforded compound **17a** which can subsequently be converted to **4b** by reduction and cyclization. The steric hindrance effect of the adjacent methyl group probably resulted in the high anti stereoselectivity of **4b**.[12] Following the same procedure as for the synthesis of **4b**, compound **4c** was synthesized using (R)-4-benzyl-2-oxazolidinone as auxiliary.

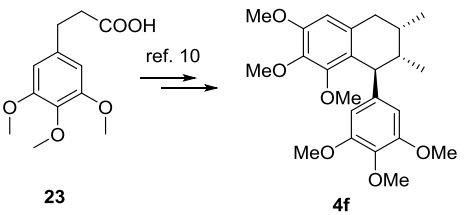


Scheme 2. Synthesis of compounds **4b** and **4c.** Reagents and conditions: (a) Pivaloyl chloride, Et_3N, LiCl, THF, −78°C to rt, for **13a**: 83%, for **13b**: 77%; (b) NaHMDS, MeI, THF, −78°C, 1h, for **14a**: 90%, for **14b**: 71%; (c) $LiOH{\cdot}H_2O$, H_2O_2, THF, 0°C to rt, for **15a**: 63%, for **15b**: 79%; (d) DIPEA, HATU, HOBT, N,O-Dimethylhydroxylamine hydrochloride, DMF, for **16a**: 82%, for **16b**: 72%; (e) *n*-BuLi, THF, −78°C, for **17a**: 73%, for **17b**: 73%; (f) $NaBH_4$, MeOH, rt, for **18a**: 73%, for **18b**: 74%; (g) HF-pyridine, CH_3CN, rt, for **4b**:71%, d.r. > 19:1, for **4c**: 78%, d.r. > 19:1, diastereomeric ratio of **4b** and **4c** were evaluated by ^{1}H NMR analysis.

Compounds **4d** and **4e** were obtained using the same method as reported for the synthesis of (+)-galbulin **3** (Scheme 3) and target compound **4f** was synthesized following the synthetic route for (+)-Isogalbuline **2** (Scheme 4).

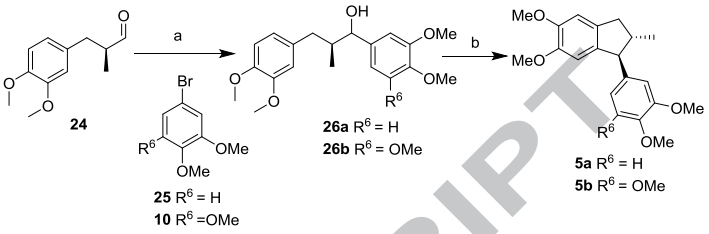


Scheme 3. Synthesis of compounds **4d** and **4e.** Reagents and conditions: (a) *n*-BuLi, THF, −78°C, for **22a**: 75%, for **22b**: 72%; (b) HF-pyridine, CH_3CN, rt, for **4d**: 75%, d.r. > 19:1, for **4e**: 80%, d.r. > 19:1, diastereomeric ratio of **4d** and **4e** were evaluated by ^{1}H NMR analysis.



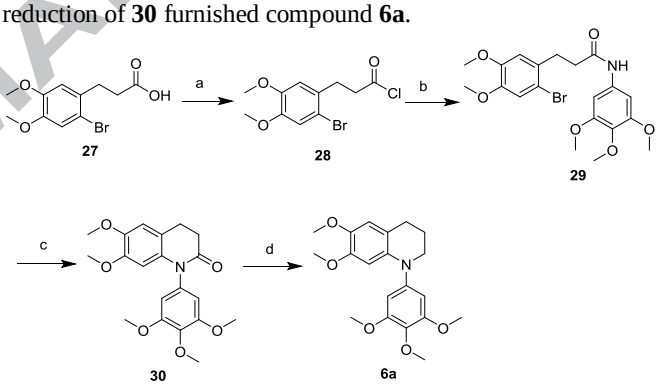
Scheme 4. Synthesis of compound **4f.**

With analogues **4** in hand, we next turned our attention onto the preparation of analogues **5**. The target compounds **5a** and **5b** were synthesized from known compound **24**.[10] Nucleophilic addition reaction of **24** with substituted bromobenzene, followed by cyclization gave the compounds **5a** and **5b** (Scheme 5).



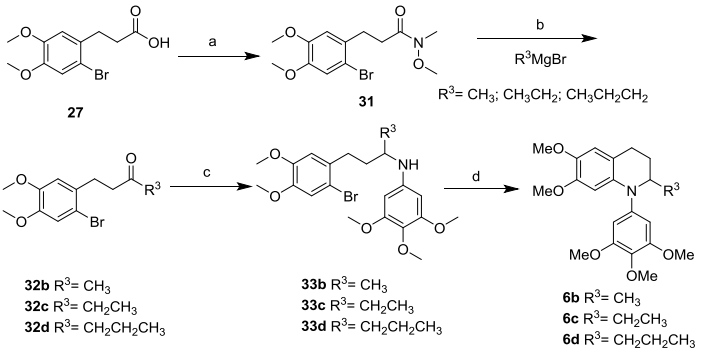
Scheme 5. Synthesis of compound **5a** and **5b.** Reagents and conditions: (a) *n*-BuLi, THF, 53%; 71%; (b) HF-pyridine, CH_3CN, rt, for **5a**: 72%, d.r. > 19:1, for **5b**: 75%, d.r. > 19:1, diastereomeric ratio of **5a** and **5b** were evaluated by ^{1}H NMR analysis.

Next, we embarked on the synthesis of analogues **6**. The synthetic strategies to access analogues **6** are described in Scheme 6-7. The target compound **6a** was prepared from the starting material **27** (Scheme 6). After the preparation of corresponding acyl chloride **28**, and subsequent condensation reaction, amide **29** was produced in high yield. An Ullmann reaction[13] of **29** with CuI produced compound **30**. Finally, reduction of **30** furnished compound **6a**.



Scheme 6. Synthesis of compound **6a.** Reagents and conditions: (a) $SOCl_2$, reflux, 6 h, 90%; (b) 3,4,5-trimethoxyaniline, Et_3N, CH_2Cl_2, 0°C to rt, 81%; (c) CuI, K_2CO_3, DMF, reflux, 4h, 64%; (d) $BF_3{\cdot}Et_2O$, $BH_3{\cdot}Me_2S$, THF, 65%.

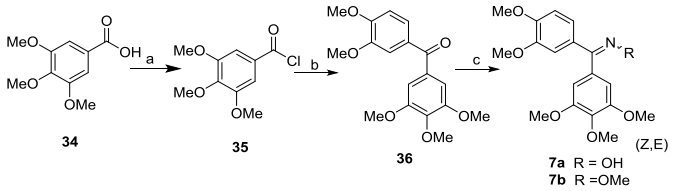
Compounds **6b**-**6d** were also prepared from **27** using a new synthetic strategy (Scheme 7). Grignard reaction of **31** with methyl, ethyl, or propylmagnesium bromide gave compounds **32b**, **32c**, and **32d**. A reductive amination, followed by a Buchwald-Hartwig cross-coupling reaction produced **6b**, **6c** and **6d** in moderate yield.[14,15]



Scheme 7. Synthesis of compounds **6b-6d.** Reagents and conditions: (a) DIPEA, HATU, HOBT, N, O-Dimethylhydroxylamine hydrochloride, DMF, 90%; (b) R_3MgBr, THF, 0°C, for **32b**: 60%; for **32c**: 55%; for **32d**: 55%; (c)

3,4,5-trimethoxyaniline, sodium triacetoxyborohydride, acetic acid, CH_2Cl_2, for **33b**: 50%; for **33c**: 40%; for **33d**: 35%; (d) $Pd(PPh_3)_4$, K_2CO_3, toluene, for **6b**: 82%; for **6c**: 78%; for **6d**: 82%.

Compounds **7a** and **7b** were synthesized from Gallic acid trimethyl ether **34** (Scheme 8). Acyl chloride **35**, obtained from compound **34**, was converted to compound **36** through a Friedel–Craft reaction. Treatment of **36** with hydroxylamine hydrochloride or methoxyamine hydrochloride gave the compounds (Z, E)-**7a** and (Z, E)-**7b**.



Scheme 8. Synthesis of compounds **7a and 7b.** Reagents and conditions: (a) $SOCl_2$, reflux, 6h, 92%; (b) $AlCl_3$, CH_2Cl_2, 41%; (c) $RONH_2$.HCl, AcONa, MeOH, for **7a**: 60%; for **7b**: 58%.

To evaluate the anti-HIV activity of the SG-1 derivatives, all the synthesized compounds, including the two described natural products and compound **37** (an intermediate of Gantacurium Chloride, commercially known as (±)-Cryptostyline III), were tested using vesicular stomatitis virus glycoprotein (VSV-G)/HIV-1 infection assay with Nevirapine as a positive control.[16,17] As indicated in Table 1, **4b** showed the most potent inhibitory activity against HIV-1 (IC_{50} 0.09 μM) with compounds **2**, **4f**, **6b, 6c** and **5b** also showing impressive submicromolar IC_{50} values against HIV-1. Compounds **4a**, **4c**, **6a**, **6d**, and **5a** however showed much less inhibitory activity, with IC_{50} values in the micromolar range. All other analogues tested exhibited no obvious activities when tested up to a 10 μM concentration. This data illustrates some clear SAR trends: (i) the methyl group at C-8 is not necessary for activity (**1** versus **4b**); (ii) The S configurations at C8' and C7' are essential for inhibition of HIV-activity (**2** versus **3; 4b** versus **4c**); (iii) The 5'-OMe group in aromatic ring B improved HIV inhibitory activity (**2, 3** versus **1; 5a** versus **5b**), however, the 3-OMe group in ring A decreases the observed activity against HIV (**4f** versus **1**); (iv) The "C" cycle can tolerate major change, with inhibition maintained when either a C atom at 7'-position was substituted by N atom or reducing the size of the ring itself, (**4** (**Series I**) versus **5** (**Series II); 5 (Series II**) versus **6** (**Series III**)). Finally, we observed a concurrent reduction in activity when the C ring is completely removed (**4** (**Series I**), **5** (**Series II**), **6** (**Series III**) versus **7** (**Series IV**)).

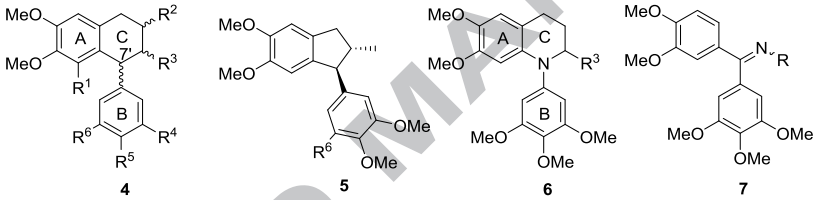


Table 1.
Antiviral activities of (+)-SG-1(**1**) and its derivatives against wild-type HIV-1.[a]

Comp.	R^1	R^2	R^3	R^4	R^5	R^6	R	Configuration of 7'	IC_{50}(μM)	95% confidence intervals (μM)
1	H	(S)-CH_3	(S)-CH_3	OMe	OMe	OMe		S	0.16	0.11-0.24
2	H	(S)-CH_3	(S)-CH_3	OMe	OMe	H		S	0.86	0.47-1.53
3	H	(S)-CH_3	(R)-CH_3	OMe	OMe	H		R	>10	-
4a	H	H	H	OMe	OMe	OMe		(±)	6.71	Wide
4b	H	H	(S)-CH_3	OMe	OMe	OMe		S	0.09	0.04-0.18
4c	H	H	(R)-CH_3	OMe	OMe	OMe		R	1.02	0.58-1.82
4d	H	(S)-CH_3	(R)-CH_3	OMe	OMe	OMe		R	>10	-
4e	H	(S)-CH_3	(R)-CH_3	-OCH_2-	-OCH_2-	H		R	>10	-
4f	OMe	(S)-CH_3	(S)-CH_3	OMe	OMe	OMe		S	0.69	0.50-0.92
5a						H		S	4.42	Wide
5b						OMe		S	0.34	Wide
6a			H					(±)	4.96	Wide
6b			Me					(±)	0.94	0.56-1.55
6c			Et					(±)	0.72	Wide
6d			Pr					(±)	1.28	Wide
30			=O						>10	-
7a							OH		>10	-
7b							OMe		>10	-
36									>10	-
37									>10	-
Nevirapine									0.013	0.008-0.018

[a] There was no cytotoxicity observed for all tested compounds at the final concentration of 10 μM.

Since the approval of Zidovudine (AZT) in 1987, 26 HIV drugs are currently used in the clinic. Combination antiretroviral (ARV) therapy is the standard treatment for HIV infection. However, emergence of resistance to this ARV regimen poses a significant challenge to the successful treatment of HIV. WHO reported that HIV resistance to ARV drugs was identified in 95% of people with HIV in developing countries.[18] As the efficacy of active compounds to resistant virus is an important parameter, we tested the effects of compounds **4b**, **4c**, **4f**, **2**, **6b** and SG-1 on three representative NNRTI-resistant HIV strains which carry mutations in RT as K103N, Y181C, and E138K/M184V.

HIV-1 carries RT-K103N, the most common NNRTI-resistance mutation, among 138,560 clinical isolates with an 8.36% of isolates containing this RT-K103N mutation.[19] K103 is located distal to the RT active site and is found on the loop connecting β5 and β6 in the RT p66 subunit located at the entrance of NVP and EFV binding pockets. As a non-polymorphic mutation, RT-K103N reduces the efficacy of first generation NNRTI by up to 100 fold. As shown in Table 2, the activities of the 5 tested compounds and SG-1 against HIV-RT-K103N were similar to those observed for wild type HIV-1, while this mutant HIV-1 reduced NVP susceptibility by 70-fold.

HIV-1 RT Y181C is the second most common mutation. It causes virus resistance to NVP (more than 50-fold), EFV (2-fold), ETR (5-fold), and RPV (3-fold).[20] We therefore tested compounds **4b**, **4c**, **4f**, **2**, **6b** on HIV-RT-Y181C replication; and none of the compounds tested exhibited any inhibitory activity up to a concentration of 10 μM (Table 2). This indicated that Y181 is a critical residue for SG-1 derivatives' interaction with RT and plays a crucial role in blocking its binding.

As previously mentioned, HIV-1 RT containing E138K/M184V routinely lead to therapeutic failure in patients treated with RPV, FTC, and TDF. Furthermore, RT-E138K/M184V also has higher processivity than the wild type RT, which results in the mutant virus having a higher replication capacity.[21] We therefore tested compounds **4b**, **4c**, **4f**, **2** and **6b** on HIV-RT-E138K/M184V replication which showed that this mutant virus conferred 4.7 to 9.1-fold resistance to **4c**, **4f**, **2** and **6b**, but only exhibited slight resistance to **4b** (2-fold) which was better than SG-1(8.6-fold).

Table 2
Inhibitory effects of SG-1 (**1**), **4b**, **4c**, **4f**, **2**, **6b** and the references NVP and 3TC on wild-type and NNRTI-resistant HIV-1 replication.

Comp.	HIV-1 wt IC_{50} (μM)	HIV-1RT-K103N			HIV-1RT-Y181C			HIV-1RT-E138K, M184V		
		IC_{50} (μM)	95% confidence intervals (μM)	Folds	IC_{50} (μM)	95% confidence intervals (μM)	Folds	IC_{50} (μM)	95% confidence intervals (μM)	Folds
1	0.16	0.18	0.13-0.27	1.1	10.8	Wide	67.5	1.38	0.65-7.26	8.6
4b	0.09	0.15	0.08-0.26	1.7	> 10	-	>111	0.18	0.11-0.28	2.0
4c	1.02	1.73	1.25-2.53	1.7	> 10	-	>9.8	7.13	Wide	7.0
4f	0.69	0.76	0.62-0.93	1.1	> 10	-	>14.5	5.91	5.28-6.57	8.6
2	0.86	1.38	0.73-2.93	1.6	> 10	-	>11.6	4.02	Wide	4.7
6b	0.94	1.40	0.82-2.64	1.5	> 10	-	>10.6	8.53	Wide	9.1
NVP	0.013	0.91	0.81-1.02	70	2.86	1.08-6.50	220	0.022	0.015-0.032	1.7
3TC	0.51	ND	ND	-	ND	-	-	>10	-	>19.6

In summary, a series of potent HIV-1 reverse transcriptase inhibitors were designed and synthesized. Compound **4b** showed potent inhibitory activity against HIV-1 with an IC_{50} of 0.09 μM. In addition, five compounds **2**, **4c**, **4f**, **6b, 6c** and **5b** also showed impressive submicromolar IC_{50} values against HIV-1. These results have established preliminary SAR trends and the activities of the 5 tested compounds and SG-1 against HIV-RT-K103N were similar to those observed for wild type HIV-1, while this mutant HIV-1 reduced NVP susceptibility by 70-fold. Furthermore, this mutant virus (HIV-RT-E138K/M184V) conferred 4.7 to 9.1-fold resistance to **4c**, **4f**, **2** and **6b**, but only slightly resistance to **4b** (2-fold) which was better than SG-1.

Acknowledgments

This work was financially supported by the National Natural Basic Research Program of China (Nos. 81473256, 81273561), the CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1-014 and No. 2016-I2M-3-009), the Beijing Key Laboratory of New Drug Mechanisms and Pharmacological Evaluation Study (No. BZ0150), the National Science and Technology Major Project (No. 2015ZX09102-023-004), and the Science and Technology Program of Beijing (No. Z151100000115008).

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Highlights

• A series of potent HIV-1 reverse transcriptase inhibitors were synthesized.
• Compound **4b** showed potent inhibitory activity against HIV-1(IC_{50} 0.09 μM).
• These results in the paper have established preliminary SAR trends.
• RT- E138K/M184V mutant virus conferred 2-fold resistance to **4b** (better than SG-1).

Graphical Abstract

Design, synthesis and biological evaluation of substituted (+)-SG-1 derivatives as novel anti-HIV agents

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